15th Annual Meeting
International Behavioural and Neural Genetics Society

I·B·A·N·G·S

International Behavioural and Neural Genetics Society

May 20-24, 2013

Leuven, Belgium

Genes, Brain and Behaviour 2013

15th Annual Meeting
International Behavioural and Neural Genetics Society

May 20-24, 2013

Leuven, Belgium
Europe

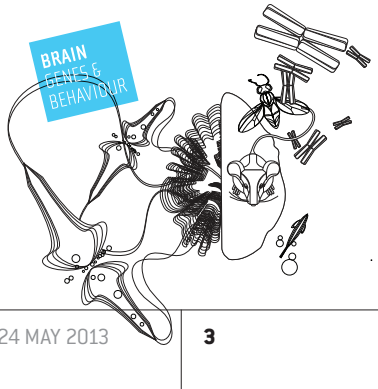


Table of Contents

Local Organizing Committee 2013 Annual Meeting

Fred Van Leuven
Gabriela Casteels

Programme Committee 2013 Annual Meeting

Fred Van Leuven, Chair
Gabriela Casteels
Chris Janus
Igor Ponomarev
Mary-Anne Enoch
Molly Cummings
Paul Shaw
Wim Crusio
Josh Dubnau, President

SPONSORS

National Institute on Alcohol Abuse and Alcoholism (NIAAA)
www.niaaa.nih.gov

LRD
http://lrd.kuleuven.be/

TSE systems
http://www.tse-systems.com

Janssen Pharmaceutica NV
http://en.janssenpharmaceutica.be/

reMYND
www.remynd.com

SATELLITE SYMPOSIUM

MONDAY **MAY 20**

08:00 **Registration**

Lemaire room

SATELLITE SYMPOSIUM LEGTEGG

09:00 ▸ **Fred Van Leuven**: Welcome

09:15 ▸ **Richard Morris:** Rapid forgetting
Edinburgh

10:00 ▸ **Markus Tolnay:** Spreading tauopathy
Basel

Willem van Croy

10:45 **Coffee break**

11:15 ▸ **V. Hugh Perry:** Impact of inflammation
Southampton

12:00 ▸ **Lennart Mucke:** Therapy aimed @ Networks
San Francisco

Lemaire room

13:00 **Lunch** offered by LEGTEGG

14:00 ▸ **Isabelle Mansuy:** Epigenetics of behavior
Zurich

14:45 ▸ **Mara Dierssen:** "Down" into Alzheimer's
Barcelona

15:30 ▸ **Joachim Herz:** The apoE-conundrum
Dallas

Willem van Croy

17:00-19:00 **IBANGS** Welcome Reception

Reception
Faculty Club Infirmerie

SPEAKERS

RICHARD MORRIS / Univ. Edinburgh

Professor of Neuroscience. Richard is best known for his "water-maze" as hippocampus-dependent L&M task for rodents. His research interests remain in neurobiology of learning and memory, as affected by amyloid in Alzheimer's. He also devotes time to public awareness and the education of school-kids.

MARKUS TOLNAY / Univ. Basel

Professor of Neuropathology. He combines academic teaching with clinical duties as a pathologist and with basic research on mechanisms underlying Alzheimer's and other neurodegenerative diseases. Markus has a long-standing interest in prion diseases and tauopathies.

V. HUGH PERRY / Univ. Southampton

Professor of Experimental Neuropathology
His CNS Inflammation research group aims to define how inflammation contributes to the outcome of neurological disease. Hugh wants to understand underlying mechanisms and helps develop therapies for acute and chronic neurodegenerative disorders.

LENNART MUCKE / San Fransisco

Founding Director of the Gladstone Institute of Neurological Disease. His research focuses on memory loss and neurological deficits in Alzheimer's disease and related disorders. Lennart's group generated informative experimental models, identified novel mechanisms and developed strategies to block neurological decline. Besides his research, he established a vigorous training program in disease-focused neuroscience.

ISABELLE MANSUY / Univ. / ETH Zürich

Professor in Molecular Cognition. Isabelle studies the genetic and epigenetic basis of cognitive functions and behavior, and the mechanisms underlying the epigenetic inheritance of complex brain functions in animal models. Her research has tight links to clinical aspects, in particular to psychiatry.

MARA DIERSSEN / Univ. Barcelona

Head of Neurobehavioral lab (Genes & Disease program, Center Genomic Regulation, Barcelona). Her research interests are in behavioral neuroscience & neurobiology of disease, interweaving experimental psychology and behavioral neuroscience. Mara developed technologies for mouse phenotyping, integrated in the Behavioral Phenotyping Platform.

JOACHIM HERZ / Univ. Texas, Dallas

Professor of Molecular Genetics and Neuroscience, and Thomas O. Hicks Family Distinguished Chair in Alzheimer's Disease Research. His research focuses on the LDL receptor gene family as signaling receptors in brain and vascular wall. Joachim's group studies the role of ApoE4, the most important genetic risk factor in sporadic Alzheimer's disease.

LEGTEGG
SATELLITE
SYMPOSIUM
ALZHEIMER'S
DISEASE
MONDAY 20 MAY 2013

▼ TUESDAY MAY 21

08:00 **Breakfast** *M.M. Van Hamaele*

09.00

OUTSTANDING TRAVEL AWARDEES

► Zhengzheng Liang
Krista Mitchnick
David Linsenbardt (symposium speaker)
Camron Bryant

Willem van Croy

15 min. **Coffe break**

10:30

SYMPOSIUM I

Comparative Behaviour Genetics: Selected vignettes from five species
► Josh Dubnau - Cold Spring Harbor, NY

Willem van Croy

12:30 **Lunch on your own**

14:00

YOUNG INVESTIGATOR LECTURE

► Judith Homberg

DISTINGUISHED SCIENTIST LECTURE

► Robert Gerlai

Willem van Croy

16:30-18:30

POSTER SESSION with local food and beer

Jubileum zaal KU Leuven

WEDNESDAY MAY 22

08:00 **Breakfast** *M.M. Van Hamaele*

09.00

PRESIDENTAL LECTURE

Bending the not so simple mind of the fly
- Scot Waddell
  University of Oxford

Willem van Croy

15 min. **Coffe break**

10:30

SYMPOSIUM II

Using Zebrafish to explore how genes ... generate behavior
- Caroline Brennan

Willem van Croy

12:30 **Lunch on your own**

14:00

SYMPOSIUM III

Novel Mechanisms in Anxiety and Depression
- Stephanie Dulawa

Willem van Croy

16:00

SYMPOSIUM IV

Hippocampus and cognitive spatial maps: Multi – Species Comparison
- Hans-Peter Lipp
- Chris Janus

Willem van Croy

MEETING PROGRAMME

▼ THURSDAY MAY 23

08:00 — **Breakfast** — *M.M. Van Hamaele*

09.00

KEYNOTE LECTURE

Neural mechanisms of genetic and environmental risk for mental disorders

- ▶ Andreas Meyer-Lindenberg
  Heidelberg / Mannheim

Willem van Croy

15 min. **Coffe break**

10:30

SYMPOSIUM V

Genetic Regulation of Ethanol Sensitization in Flies, Mice, Humans

- ▶ Stephen Boehm
- ▶ Tamara Phillips

Willem van Croy

12:30 — **Lunch on your own**

14:00

SELECTED TALKS SESSION I

- ▶ Nicod Jerôme
  Leonard Schalwyk
  Dai Stephens
  Andre Pietrzykowski
  Brunno van Swinderen
  Gang Chen
  Dana Most

Willem van Croy

16:00

GENERAL BUSINESS MEETING

All participants are welcome

Willem van Croy

18:20-20:00

Banquet

Faculty Club Infirmerie

FRIDAY MAY 24

08:00 **Breakfast** *M.M. Van Hamaele*

09.00

SELECTED TALKS SESSION II

- Jorge Campusano
  Tsuyoshi Miyakawa
  Maarten Loos
  Kyung-An Han;
  Marie-L Samson
  Margarita Alfimova
  Stephen Ekker

Willem van Croy

15 min. **Coffe break**

11:00

SYMPOSIUM VI

Epigenetics of brain disorders: Focus on alcoholism

- Igor Ponomarev
- Antonio Noronha

Willem van Croy

13:00

MEETING ADJOURNED

TUESDAY
MAY 21

OUTSTANDING TRAVEL AWARDEES

Molecular basis of scouting behaviors in honey bees

ZS Liang[1], T Nguyen[2], HR Mattila[3], SL Rodriguez-Zas[1,4], SR Bruce[4], TD Seeley[5], GE Robinson[1,2,6]

Division of labor among honey bee foragers involves "scouts" and "recruits." Scouts seek new food sources or nest sites independently while recruits wait in the hive to be informed about the location of good food or nest sites. We hypothesized that scouting behavior in honey bees is analogous to novelty-seeking behavior in vertebrates, and is therefore associated with differences in brain dopaminergic, octopaminergic and glutamatergic systems. We found significant brain down-regulation of the D1-type dopamine receptor genes and upregulation of the octopamine receptor genes in scouts compared to non-scouts. Microarray analysis confirmed these findings and further implicated glutamatergic and GABAergic neurotransmitter systems. Oral pharmacological treatments using glutamate or octopamine both increased the probability of scouting, while dopamine antagonists decreased it. Blocking glutamate vesicle transport inhibited the behavioral effect of glutamate. We further hypothesized that scouts who seek food sources and those who seek nest sites would share a common "molecular signature" in their brains. Behaviorally analysis showed that nest-site scouts were 3.4 times more likely to seek food sources later, and they shared a minimum of 89-gene expression profiles that predicted individual behavior with high accuracy. These findings illustrated how individual differences in behavior can arise from the differences in gene regulation, and demonstrate intriguing similarities in human and insect novelty seeking, subserved by conserved molecular components. Shared molecular signatures of scouting behaviors across ecological contexts also supported the scouting tendency as an "animal personality" and provide a molecular standpoint to study the evolution of limited plasticity in animal behavior.

[1] Neuroscience Program
[2] Institute of Genomic Biology, University of Illinois at Urbana-Champaign
[3] Department of Biological Sciences, Wellesley College
[4] Department of Animal Sciences, University of Illinois at Urbana-Champaign
[5] Department of Neurobiology and Behavior, Cornell University
[6] Department of Entomology, University of Illinois at Urbana-Champaign

Support: NSF Frontiers in Biological Research grant EF 0425852 (B.L. Schatz, PI, BeeSpace Project), NIH Director's Pioneer Award 1DP10D006416 (G.E.R) and the Illinois Sociogenomics Initiative (G.E.R). USA.

OUTSTANDING TRAVEL AWARDEES

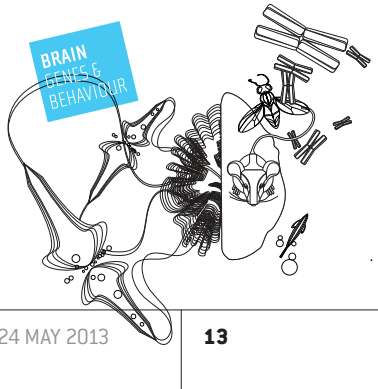
Dissociating epigenetic mechanisms of memory in the hippocampus and perirhinal cortex of rats

Krista A Mitchnick[1, 3], Mathew O'Hara[1, 3], Bettina E Kalisch[2, 3] & Boyer D Winters[1, 3]

Recent research has demonstrated that the epigenetic mechanisms of DNA methylation and histone acetylation work in concert to subserve long-term memory. Much of this work has used the contextual fear conditioning paradigm. In the current study, we investigated the role of DNA methylation and histone acetylation in both the hippocampus (HPC) and perirhinal cortex (PRh) of rats using the object-in-place (OIP) paradigm, a task that relies on both the targeted regions. An inhibitor of the histone acetyltransferase CBP (C-646) significantly impaired long-term OIP memories when infused directly into the HPC or PRh immediately following object encoding, whereas non-selective DNA methylatransferase (DNMT) inhibitors (5-AZA, RG-108) disrupted long-term OIP memory only when infused into the HPC. Subsequent experiments are evaluating the effects of selective DNMT inhibition within the HPC, as different DNMTs have been shown to methylate in a preferential fashion, i.e., de novo (DNMT3a, DNMT3b) versus maintenance (DNMT1) methylation. Early results from this work indicate that small interfering RNA targeting the de novo DNMT3a in the HPC disrupts long-term OIP memory. Accordingly, preliminary molecular findings are suggestive of DNMT3a upregulation in the HPC, but not PRh, following the OIP sample phase. These results, therefore, indicate a dissociation between epigenetic mechanisms for memory in different brain regions and suggest that DNA methylation and histone acetylation processes need not always operate in tandem to mediate memory storage. Moreover, our findings highlight the importance of de novo DNA methylation in HPC-dependent memory.

[1] Department of Psychology
[2] Department of Biomedical Sciences
[3] Collaborative Neuroscience Program, University of Guelph, Guelph, ON, Canada

Funding: NSERC



TUESDAY
MAY 21

OUTSTANDING TRAVEL AWARDEES

Determining the heritability of locomotor sensitization to ethanol and its relationship to ethanol's positive motivational effects in mice

David N. Linsenbardt[1] & Stephen L. Boehm II[1]

Sensitization to the locomotor stimulant effects of alcohol (ethanol) is thought to be a heritable risk factor for the development of alcoholism that reflects progressive increases in the positive motivational effects of this substance. However, very little is known about the genetic influences involved in this phenomenon or the extent to which ethanol's positive motivational effects are altered in parallel to its development. The first goal of this work was to determine the heritability of ethanol-induced locomotor sensitization using short-term behavioral selection. C57BL/6J (B6) x DBA/2J (D2) F2 mice were phenotyped for the expression of locomotor sensitization, and bred for high (HLS) and low (LLS) expression of this behavior. A secondary goal was to characterize possible line differences in ethanol's positive motivational effects using conditioned place preference (CPP) and a limited access voluntary ethanol consumption assay known as Drinking-in-the-Dark (DID). Genetic differences accounted for 22% (h2=.22) of the observed line differences in locomotor sensitization. However, whereas there were no significant differences in CPP between lines, there were marginal differences (p=.06) in ethanol consumption (albeit in females only) with LLS mice generally consuming more ethanol than HLS mice. That changes in ethanol sensitivity following repeated exposures are in part genetically regulated highlights the relevance of studies aimed at determining how genes regulate susceptibility to ethanol-induced behavioral and neural adaptations. Additionally, line differences in ethanol intake but not ethanol-induced CPP suggest that the utility of locomotor sensitization as a model of alterations in ethanol's positive motivational effects in mice is still unclear.

[1] Indiana Alcohol Research Center and Department of Psychology, Indiana University – Purdue University Indianapolis, Indianapolis, IN 46202.

Acknowledgments: This work was funded by NIAAA grant #s AA015434 (SLB), AA016789 (SLB), and AA07462 (DNL).

OUTSTANDING TRAVEL AWARDEES

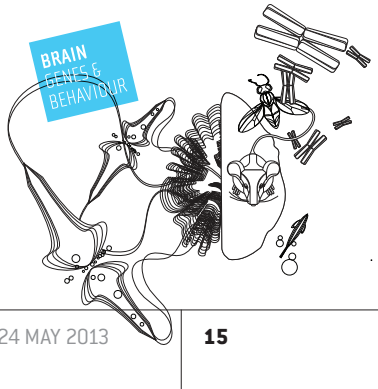
Rufy1 or Hnrnph1 is a likely quantitative trait gene for methamphetamine sensitivity

Camron D. Bryant[1,2], Clarissa C. Parker[3], Michael A. Guido[3], Loren A. Kole[3], Lisa Goldberg[1], Stacey Kirkpatrick[1], Greta Sokoloff[3], Jackie E. Lim[3], Riyan Cheng[3], Abraham A. Palmer[3,4]

Sensitivity to the locomotor stimulant properties of drugs of abuse is a heritable trait and its genetic basis may be shared with alleles that modulate activation of the mesolimbic reward pathway. We previously used mouse lines derived from C57BL/6J and DBA/2J alleles that were selected for high and low methamphetamine (MA) sensitivity and identified a genome-wide significant quantitative trait locus (QTL) on chromosome 11. In order to further pursue this QTL, we utilized the power of an F2 cross and the iterative nature of interval-specific congenic lines in an effort to identify the causal gene(s) underlying this QTL. The results of F2 mice and the larger congenic lines revealed two large-effect QTLs for MA-induced locomotor activity; however, the phenotypic results of the smaller subcongenic lines revealed additional smaller effect QTLs with different modes of inheritance. One subcongenic locus converged remarkably well with the QTL peak in the F2 cross and altered methamphetamine sensitivity in a time-dependent manner. We generated eight sub-subcongenic lines derived from this subcongenic line (17 congenic lines total). Owing to a fortuitous recombination event, we identified and replicated a 0.23 Mb region spanning 50.17-50.40 Mb that was critical for MA sensitivity. This region contains only three genes (Rufy1, Hnrnph1, and Cby3) and only two of these genes are expressed in the brain (Rufy1 and Hnrnph1). This study exemplifies how a careful and detailed use of congenic lines can yield narrow QTL intervals and a tractable number of genes for quantitative trait gene identification.

[1] Laboratory of Addiction Genetics, Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine
[2] Department of Psychiatry, Boston University School of Medicine
[3] Department of Human Genetics, The University of Chicago
[4] Department of Psychiatry and Behavioral Neuroscience, The University of Chicago

Support: R01DA021336, R00DA029635, T32GM008541



TUESDAY
MAY 21

SYMPOSIUM I

COMPARATIVE BEHAVIOUR GENETICS: SELECTED VIGNETTES FROM FIVE SPECIES

CHAIR: JOSH DUBNAU

GHOLSON LYON
Clinical Genetics of Neuropsychiatric Disorders

PATRIK VERSTREKEN
Post translational modification of synaptic active zones in the modulation of behavioral and activity defects in a fly ALS mode

JOSH DUBNAU
The Transposon Storm: from Barbara McClintock to Lou Gehrig

BAMBOS KYRIACOU
Molecular and neurogenetic basis of biological rhythms in an intertidal crustacean

Clinical Genetics of Neuropsychiatric Disorders

Gholson Lyon

The currently classified syndromes of schizophrenia, obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), autism and other mental illnesses are quite heterogeneous between families, and their symptoms can be seen in known single locus disorders such as Fragile X and 22q11.2 velocardiofacial syndrome. I will discuss progress with microarrays and next generation sequencing for the analysis of large families in Utah with and without idiopathic intra-familial neuropsychiatric syndromes.

Post translational modification of synaptic active zones in the modulation of behavioral and activity defects in a fly ALS mode

Patrik Verstreken

Expression of clinical TDP43 mutant proteins in fruit flies result in activity and behavioral defects. While the underlying molecular mechanisms remain elusive, specific post translational modifications of active zone associated proteins are a promising strategy in mitigating these ALS-associated defects.

The Transposon Storm: from Barbara McClintock to Lou Gehrig

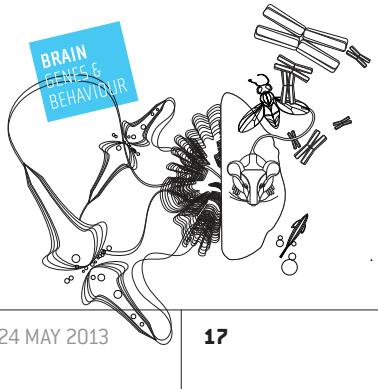
Josh Dubnau

Transposable elements (TEs), first discovered by Barbar McClintock, are mobile genetic elements that constitute as much as 50% of mammalian genomes and 30% of the Drosophila genome. Both animals and plants have evolved formidable mechanisms to silence TEs in the germline in order to preserve the integrity of the genome. The re-awakening of these jumping genes in the germline is in fact so disastrous that it leads to the ultimate destruction of the tissue leading to sterility. We will show evidence that TEs also are re-awakened in the brain both with normal aging and associated with neurodegenerative disorders. Our evidence derives both from experimental work in fruit flies and from bioinformatic analyses of deep sequencing datasets from fly, mouse, rat, and human.

Molecular and neurogenetic basis of biological rhythms in an intertidal crustacean

Bambos Kyriacou

The molecular basis of 24 h circadian rhythms in behaviour is well established in terrestrial model eukaryotes, and is composed of a series of interconnected feedback loops that in Drosophila are present in a restricted set of neurons. However, next to nothing is known about the tidal clock which dominates the behaviour of intertidal organisms and has a period of 12. 4 hours. I will describe how we have uncovered the molecular and neurogenetic principle underlying how circadian and tidal clocks work in the sea louse, Eurydice pulchra.



TUESDAY
MAY 21

YOUNG INVESTIGATOR LECTURE

Serotonin transporter gene variation in rats: for better and for worse

Judith R Homberg[1]

Mainstream psychiatric research is focussing on understanding how genes and environmental components interact in shaping behaviour. The human serotonin transporter promoter polymorphism (5-HTTLPR) is a model par example for gene x environment (GXE) interactions in psychiatry. It is associated with trait anxiety and increased risk for depression in the context of early life stress. Yet, along with the view that common polymorphisms will only be maintained across evolution when having beneficial consequences for the human population, recent studies have revealed that the 5-HTTLPR is associated with a decreased risk for depression under favourable environmental conditions, as well as various cognitive improvements. It is our aim to understand more precisely under what environmental conditions the 5-HTTLPR mediates 'for better' and 'for worse' behavioural manifestations. To this end we are using serotonin transporter (5-HTT) knockout rats. The animals show increased anxiety and depression-related phenotypes, as well as cognitive improvements. Our studies reveal that 5-HTT knockout rats are sensitive to both rewarding and aversive environmental stimuli, based on which they acquire strong Pavlovian conditioned responses. When exposed to a single or uncontrollable stimulus, they engage into perseverative habitual behaviour (anxiety- and addiction-related behaviour). However, when exposed to varying or controllable stimuli, they are very flexible and adjust behaviour towards the most motivationally relevant one. This phenomenon has heuristic value for psychotherapies in the treatment of GXE psychiatric disorders. We are currently studying underlying (epi)genetic and neuroplastic mechanisms, as well as the role of developmental consequences of 5-HTT knockout versus constitutively increased serotonin levels.

[1] Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Centre, Dept Cognitive Neuroscience, Nijmegen, The Netherlands

This research is funded by the Dutch Organisation for Scientific Research, Grant # 864.10.003 awared to J. Homberg.

TUESDAY
MAY 21

DISTINGUISHED SCIENTIST LECTURE

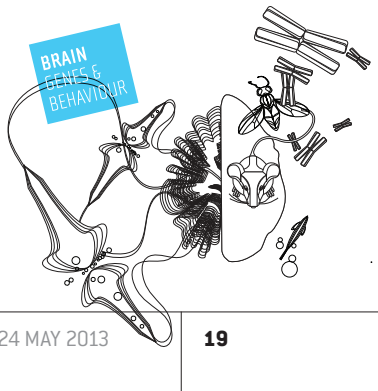
Alcohol, dopamine and social behaviour: The first steps towards a neurobehavioural genetic analysis

R. Gerlai[1]

The zebrafish is increasingly utilized in neurobehavioral genetic analysis, including in the modeling and the analysis of the mechanisms of alcohol related disorders. This small and prolific vertebrate may be an ideal tool with which the biology and genetics of CNS effects of alcohol may be studied. In this talk I review our own preliminary studies which focus mainly on the effect of alcohol on social behaviour and the potential neurochemical mechanisms underlying these effects. We have shown that the sight of live conspecifics is rewarding and the sight of animated conspecific images also induces robust shoaling (group preference). This shoaling response is blocked by a dopamine D1 receptor antagonist. Furthermore, presentation of shoaling images induces a robust increase of dopamine and DOPAC but not serotonin or 5HIAA, as measured by HPLC in the zebrafish brain. Acute alcohol administration induces shoaling but chronic alcohol treatment leads to adaptation at the behavioural level. Correlated neurochemical responses in a number of neurotransmitters and their metabolites have also been observed along with changes in gene expression as detected by semi-quantitative RT-PCR and DNA microarrays. We have also started the analysis of strain differences in these responses and found both alcohol dependent and alcohol independent strain effects in behaviour, neurochemistry and gene expression. The results as of now do not present a coherent story with clear mechanistic insights but do provide support for the use of this species in neurobehavioral genetic analysis of alcoholism. Given the target rich aspect of this research, classical forward genetic as well as newly developed reverse genetic methods will be of good use in unravelling the mechanisms underlying the complex effects of alcohol on the vertebrate brain.

[1] Department of Psychology, University of Toronto Mississauga, Mississauga, Ontario, Canada

Support: NIH/NIAAA, NSERC, Noldus Info Tech



TUESDAY
MAY 21

poster # 1

posters are presented alphabetically

Replicate line differences in ethanol drinking microstructure in High Drinking in the Dark selected mice

AM Barkley-Levenson[1], JC Crabbe[1]

The High Drinking in the Dark (HDID) mice have been selectively bred for reaching high blood ethanol concentrations (BECs) following the limited access Drinking in the Dark (DID) test. We have shown previously that mice from the first HDID replicate line (HDID-1) have larger ethanol drinking bouts than the low-drinking HS/Npt control mice (Barkley-Levenson & Crabbe, 2012). In the present study, we tested mice from the second HDID replicate line (HDID-2) and HS/Npt mice in a 4-day DID procedure to determine whether this large bout size is a correlated response to HDID selection. Adult male HDID-2 and HS/Npt mice were singly housed in shoebox cages connected to the BioDAQ Episodic Intake Monitor system (Research Diets Inc.), which continuously records the weight of the ethanol bottle. Mice received 2 hr access to 20% ethanol on Days 1-3, and 4 hr access followed by blood sampling to determine BEC on Day 4. On Day 4, HDID-2 mice had significantly greater total g/kg ethanol intake, higher BECs, more drinking bouts, and a shorter average inter-bout interval than HS/Npt mice. This drinking structure is different from that seen previously with the HDID-1s, and suggests that HDID-2 mice achieve high BECs during the DID test by drinking with greater frequency than the HS/Npt mice (i.e. more bouts, closer together) rather than drinking with greater "efficiency" (larger g/kg bout size). Thus, selection for drinking to intoxication appears to have produced two distinct patterns of consumption, both of which lead to high BECs and high g/kg intake.

[1] Portland Alcohol Research Center, Department of Behavioral Neuroscience, Oregon Health & Science University, and VA Medical Center, Portland, Oregon 97239 USA.

Funding support: NIH-NIAAA grants AA13519, AA10760, AA20245, a grant from the US Department of Veterans Affairs, and USAMRMC Grant 10234005.05. AMB-L is supported by an Oregon Health & Science University Graduate Research Scholar award

TUESDAY
MAY 21

poster # 2

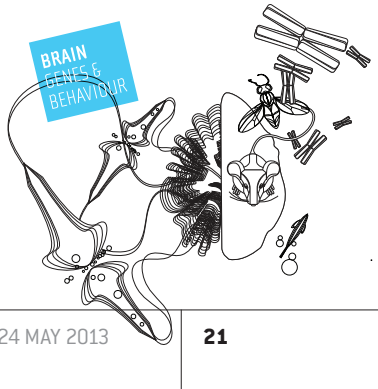
Age-related dysfunction in motor ability and motor learning in the 5xFAD mouse model of Alzheimer's Disease.

TP O'Leary[1], H Mantolino[1], DL Hestermann[1], RE Brown[1]

The 5xFAD mouse model of Alzheimer's Disease (AD) develops motor dysfunction at 9 months of age (Jawhar et al., 2012, Neurobiol. Aging, 33, 196.e29-40) and thus may be a useful model of the motor impairments which develop in AD patients.
We therefore tested male and female 5xFAD mice and wild-type controls (C57BL/6J x SJL/J F2) at 3-4, 6-7, 9-10, 12-13 and 15-16 months of age in a battery of motor behaviour tasks which included motor coordination and motor learning on the accelerating rotarod, balance on the balance- beam, and motor strength/agility on the wire-suspension and grid-suspension tests. The 5xFAD mice showed decreased body weight, and impaired motor coordination and learning on the rota-rod at 9, 12 and 15 months of age, relative to wild-type mice. The 5xFAD mice also had impaired performance on the balance beam,
grid-suspension and wire-suspension tests at 10, 13 and 16 months of age. Very few sex differences were found, except that male mice showed more variability in performance on the wire-suspension and grid-suspension tests than females.
This study demonstrates that impairments are present in motor coordination, motor learning, balance, and motor strength/agility in the 5xFAD mouse beginning at 9 months of age. These motor disabilities must be considered when using 5xFAD mice in tests of cognitive function which rely on normal motor ability (i.e. Morris water maze). We continue to investigate the neural and genetic causes of these motor dysfunctions.

[1] Departments of Psychology and Neuroscience Dalhousie University, Halifax, Nova Scotia, Canada B3H 4R2

Funding: NSERC of Canada



TUESDAY
MAY 21

poster # 3

Integrative model of genetic, neurocognitive, and psychosocial correlates of adolescent alcohol-related sexual risk behavior

Angela D. Bryan[1,3], Renee E. Magnan[2], Eric Claus[3], & Kent E. Hutchison[1,3]

Juvenile justice involved youth are at greater risk for negative outcomes of risky sexual behavior compared to the general adolescent population. Given the strong connection between alcohol use and risky sexual behavior in this population, it is important to consider underlying factors that may jointly contribute to substance use and risky sex. 172 juvenile justice involved adolescents (mean age 16 years) were genotyped for the CHRM2 SNP, the CRN1 SNP, and the DRD4 VNTR polymorphism, and a summative index was created such that higher values were associated with having more risk variants. This index was associated with variation in BOLD activation during fMRI scanning in the cerebellum, left posterior insula (LPI), right superior parietal (RSP) and the ventral tegmental area (VTA) during the balloon analog risk task (BART). These four regions served as indicators of a latent "neurocognitive activation" variable, which was associated with a latent factor of alcohol-related sex risk behavior. The full structural equation model was an adequate fit to the data, Yuan-Bentler scaled χ^2 (41, n=172) = 62.97, p<.05, CFI=.95, RMSEA=.07. Despite the cross-sectional nature of the data, the outcomes provide support for a biopsychosocial approach to our understanding of sexual risk and substance use among adolescents. Ultimately, the inclusion of neurocognitive and genetic factors in integrative models of adolescent risk behavior may assist in our understanding of the etiology of these behaviors and help to determine for whom interventions to change risk behavior may be most effective.

[1] Department of Psychology and Neuroscience, University of Colorado, Boulder
[2] Washington State University Vancouver
[3] The Mind Research Network, Albuquerque, NM

TUESDAY
MAY 21

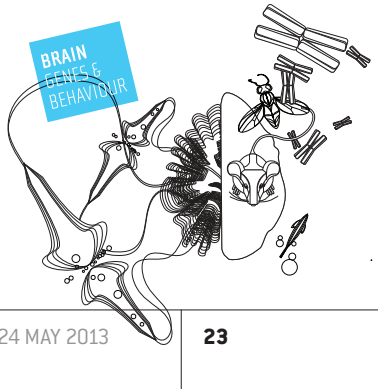
poster # 4

GeneWeaver: a Web based system for the cross-species integration of functional genomics in behavior

JA Bubier[1], JJ Jay[1,] MA Langston[2], EJ Baker[3] and EJ Chesler[1]

The plummeting cost and wide spread adoption of large-scale functional genomics studies has brought about a data deluge of sorts. Increasing amounts of large-scale genomics data are being created, the papers published and the data archived. However, much of the data exists as manuscript tables or journal supplemental appendices, or exists in disparate databases. This makes integrative use of the data to find convergent evidence for gene-gene, gene-function and function-function relations challenging if not inaccessible for most investigators. It is imperative that the data be converted into a computable format, to reap the most reward from these large primary datasets. Our curated public database GeneWeaver (www.geneweaver.org) couples curated gene lists from genomic studies to integrated combinatorial analysis tools. GeneWeaver also contains gene associations to numerous structured annotation sources (e.g. MeSH, GO, HPO, MP, KEGG) and neuroscientific databases including NIF, Allen Brain Atlas, and others. When these resources are integrated with the primary data from many individual experiments, across seven species, it serves as a powerful platform for induction. GeneWeaver tackles the difficult process of gene identifier mapping within and among species, using NCBI's Homologene as its primary means of integrating data across species. Users can upload their own primary data and privately store, retrieve and integrate this data within the GeneWeaver database. This resource can be used in a variety of methods to analyze convergent evidence for the roles of genes in behavior and through integrating functional genomics and comparative psychology to perhaps, one day, reconstruct behavior through biology.

[1] The Jackson Laboratory 600 Main Street Bar Harbor, ME 04609
[2] Department of Electrical Engineering and Computer Science, University of Tennessee, Knoxville, TN 37996, USA
[3] School of Engineering & Computer Science, Baylor University, Waco, TX 76798, USA. NIH R01AA18776 to EJC



TUESDAY
MAY 21

poster # 5

A multivariate model for the prediction of risky alcohol consumption behavior in humans. The implication of the C385A FAAH SNP and subjective evaluation of drug pictures.

K.M. Bühler[1], E. Huertas[2], V. Echeverry-Alzate[1], J. A. López-Moreno[1]

The non-synonymous Single Nucleotide Polymorphism (SNP) rs324420 causes a change from a cytosine to an adenine nucleotide at position 385 in exon 3 of the FAAH gene (C385A). This SNP has been repeatedly associated with drug-related behaviors in humans and animal models, being therefore a good candidate genetic marker for addictive disease. Recently, subjective markers like the evaluation of drug-related pictures have also been proposed as a potential biomarker for different drug consumption phenotypes.
Here we investigated the utility of integrating the C385A SNP and the drug-related picture evaluation into a multiple regression model to predict alcohol, nicotine and cannabis consumption in comparison to a bivariate model. One hundred eighty-five university students provided information of their usual drug intake using a self-report questionnaire, performed a picture-rating task (composed of neutral, drug and distractor pictures) and supplied a saliva sample for genotyping.
The bivariate model showed that the CC genotype was significantly associated with higher alcohol drinking during weekends and the presence of a positive correlation between rating of alcohol-pictures and the amount of alcohol intake. However, using the multiple regression model the slopes became more accurate and this allowed better discriminative prediction for higher alcohol consumption.
These results suggest that the FAAH enzyme might be implicated in early stages of alcohol dependence and that the C385A SNP would be useful as a genetic biomarker. Additionally, we show that multivariate models which integrate genetic and subjective marker information are more useful for the prediction of higher alcohol drinking than simpler bivariate models.

[1] Laboratory of Psychobiology, Department of Psychobiology,
[2] Laboratory of Human Experimental Psychology, Department of Basic Psychology, Faculty of Psychology, Complutense University of Madrid, Spain.

Support: Fondo de Investigación Sanitaria (Red de Trastornos Adictivos, FEDER, RD06/0001/0011, to J.A.L.M), Ministerio de Ciencia e Innovación (SAF2011-26818 to J.A.L.M.), Agencia Antidroga de la Comunidad de Madrid (Art.83- to J.A.L.M.), and The European Foundation for Alcohol Research (EA 12 21 to J.A.L.M.)

TUESDAY
MAY 21

poster # 6

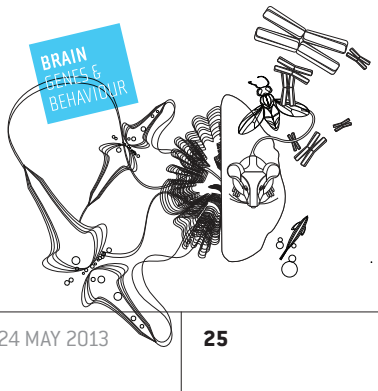
Using zebrafish to identify genetic modifiers of stress response

Tanya L. Poshusta, Randall G. Krug, Tammy. M. Greenwood, Nicole J. Boczek, Samantha L. Gardner, David P. Argue, and Karl J. Clark

Stress-induced changes in brain function and physiology contribute to neuropsychiatric disorders, a major cause of disability in the world. The genetic contribution of the stress response system (SRS) and environmental factors contribute to the progression of neuropsychiatric disorders, such as major depressive, generalized anxiety, and substance use disorders. Complex multisystem diseases require whole animal models for effective study. Using zebrafish, we created targeted germline mutations in corticotropin releasing hormone receptor 1 (crhr1) and the ACTH receptor (mc2r) using TAL-Effector Nucleases (TALENs). Importantly, mutation of mc2r blocks locomotor stimulation in our behavioral assay following hyperosmotic challenge in larval zebrafish. We are also examining the effects of crhr1 loss.
Using this larval behavioral assay, our lab is screening a panel of revertible, expression-tagged insertional mutant zebrafish that are being produced at Mayo Clinic (GBT alleles). These dominantly marked mutant alleles permit rapid screening of single gene contributions to quantitative biological traits, including behavioral genetics. Unbiased forward genetic screens, which make no assumption about the pathways involved in the vertebrate SRS, make it possible to discover genes in both suspected and unknown or unsuspected pathways. We have screened over 90 expression-selected mutant lines and have identified 5 mutant lines with a significantly altered locomotor response to hyperosmotic stress, including pbx1a, cyth3, and atp1b2a mutants. Together, these reverse and forward genetic tools are defining the genetic basis of the vertebrate stress response, which will permit advanced screening for indicators of disease potential and development of new therapies.

[1] Department of Biochemistry and Molecular Biology and the Mayo Addiction Research Center, Mayo Clinic., Rochester, MN USA

Funding Support: DA032194 and Mayo Foundation



TUESDAY
MAY 21

poster # 7

Genetic and pharmacotherapeutic modifiers of the ethanol and nicotine response in zebrafish

MA Cousin[1], AR Wiinamaki[1], TA Ristau[2], DP Argue[1], KJ Clark[1], SC Ekker[1], EW Klee[1]

Excessive alcohol consumption places a tremendous burden on US society, causing 75,000 deaths and leading to economic costs associated with alcohol problems exceeding $184 billion annually (2002 US DOJ report). Despite this impact, treatment strategies for alcohol abuse have led to only modest reductions in alcohol use in the US during the past decade, with current pharmacotherapy treatment options yielding only modest success within clinical settings (2012 US Surgeon General Report). To begin to address these problems, we have extended our larval zebrafish behavioral study of nicotine to counter-screen both genetic and pharmacotherapeutic modifiers of ethanol-induced locomotor activation.

To date, we have identified two genetic loci of interest. GBT200 attenuates ethanol-induced locomotor activation, while not effecting nicotine-induced locomotor activation. Interestingly, GBT200 does disrupt the varenicline block of nicotine response we have observed. We have also shown that Hbog, previously shown to decrease larval zebrafish locomotor response to nicotine, attenuates the larval ethanol response.

The pharmacotherapeutics we found to attenuate nicotine-induced locomotion have generated varied results when evaluated in the context of ethanol. Apomorphine and topiramate attenuate locomotor activation by both nicotine and ethanol. Disulfiram attenuates ethanol and not the nicotine response. Three benzodiazepines, betaxolol and bupropion attenuate nicotine and not the ethanol response. Varenicline attenuates the nicotine, but not the ethanol, response. This diversity of genetic and pharmacotherapeutic modulation of the locomotor responses to ethanol and nicotine indicates overlapping,
yet partially distinct mechanistic underpinnings. This interactome may explain, in part, the overwhelming coincident smoking habits of alcohol-dependent individuals.

[1] Mayo Addiction Research Center, Mayo Clinic, Rochester, MN
[2] University of Minnesota, Rochester

Funding Support: NIDA (1 F31 DA034475-01), KL2-CTSA Award, Eagles Foundation

TUESDAY
MAY 21

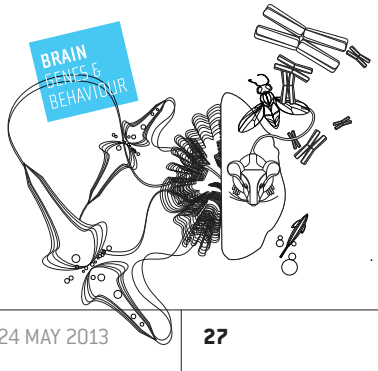
poster # 8

The quest for candidate genes affecting the hypothalamic pituitary adrenal (HPA) axis: A linkage study in an F2 cross of mice bred for trait anxiety

M Gonik[1], E Frank[1], MS Keßler[1], B Pütz[1], T Bettecken[1], B Müller-Myhsok[1], C Touma[1], R Landgraf[1], L Czibere[1]

Despite years of extensive research on a common final pathway of anxiety and depression-related disorders, it is still a major issue to pinpoint the candidate genes involved in modulating the relevant phenotypes, among others, due to the complexity of the respective traits.
To circumvent the pitfalls of analyzing a population with vast amounts of heterogenous variants, including rare ones, we followed a breeding strategy to select for genetic variants based on trait anxiety in mice. A commonly used test in antidepressant research, the elevated plus-maze, was applied to select for high (HAB) and low (LAB) anxiety-related behavior mice over generations, starting from the outbred CD-1 mouse strain. After accumulating some of the genetic determinants, we crossbred HABxLAB animals to generate a population of HABxLAB-derived F2 mice that would already show free segregation of the previously inbred alleles, thus allowing us to calculate linkages based on the phenotypes of interest.
Applying genomic single-nucleotide polymorphism (SNP) screening in these F2 mice, with subsequent linkage analyses, we succeeded in highlighting a very strong effect of a 7.5cM locus on mouse chromosome 3 on HPA-axis responsiveness, which is known to be connected with anxiety and depression scale disorders. Indeed, the locus harbors genes relevant to corticosteroid synthesis, e.g. Hsd3b1.
Using this bottleneck breeding and subsequent segregating approach, we could also demonstrate that the effect sizes can be increased to a well-measurable size of true effects in complex traits, which seems to be acceptable even at the price of losing other potential loci.

[1] Max Planck Institute of Psychiatry, Munich, Germany



TUESDAY
MAY 21

poster # 9

Whole transcriptome analysis of wheel running and alcohol behaviors in mice

Todd M. Darlington[1] and Marissa A. Ehringer[1]

Our laboratory recently reported that in C57Bl/6J mice, two-bottle choice preference for alcohol decreases when there is a running wheel present. The mesolimbic dopaminergic pathway, of which the striatum plays an important role, has been implicated in drug seeking, as well as exercise behaviors. We hypothesized that access to exercise initiates transcriptional changes in the striatum, resulting in changes in alcohol consumption. Mice were housed for 16 days under four different conditions: no wheel and water only, running wheel and water only, no wheel and alcohol/water two-bottle choice, and running wheel and alcohol/water two-bottle choice. Striatal mRNA from 24 female C57BL/6J mice was quantitatively sequenced on an Illumina HiSeq 2000. We identified 203 exercise-responsive genes, 18 alcohol-responsive genes, and 53 genes that showed an interaction effect between exercise and alcohol. Furthermore, we performed a Weighted Gene Co-expression Network Analysis and identified two exercise-responsive co-expression modules and two interaction-responsive co-expression modules. Results from differential expression and co-expression suggest potassium signaling, MAPK signaling, and glial-cell specific processes may be important in mediating the behavioral interaction between running and consuming alcohol. Furthermore, data suggest one possibility for the interaction of exercise and alcohol consumption could be that running potentially alters acute sensitivity to alcohol, leading to decrease in alcohol consumption.

[1] Department of Integrative Physiology, Institute for Behavioral Genetics, Boulder, CO USA

Support: R01 AA017889, T32 DA017637

TUESDAY
MAY 21

poster # 10

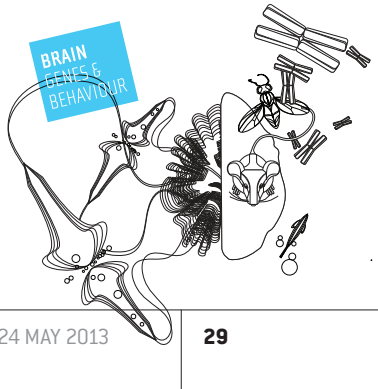
Mu-opioid receptor drug effects on methamphetamine intake in mice bred for high methamphetamine intake

EC Eastwood[1], TJ Phillips[1, 2]

Selective breeding was used to produce two replicate sets of mouse lines that consume high (MAHDR) or low (MALDR) amounts of methamphetamine (MA) in a two-bottle choice MA drinking (MADR) procedure. 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 had greater expression of Oprm1 than MAHDR mice in medial prefrontal cortex tissue. Negative genetic correlations were found between MA intake and both morphine intake and locomotor activation by MOP-r agonist drugs. We hypothesized, based on lower expression of Oprm1 in MAHDR mice, that MOP-r agonist drugs would reduce MA intake. We also examined clearance of morphine, and the MOP-r agonist drug, fentanyl, which had been used in prior studies. Morphine dose-dependently decreased MA intake during the first 4 h of a 6-h limited access drinking-in-the-dark, two-bottle choice study. No significant differences were found between the MADR lines in morphine or fentanyl levels or clearance from blood across a 2 h period, suggesting that pharmacokinetic differences do not account for their differences in response to MOP-r drugs. Human clinical trials have shown some efficacy of the partial MOP-r agonist, buprenorphine, in reducing psychostimulant abuse. Our previous data also showed reduced MA intake by buprenorphine in MAHDR mice. These results support further investigation of MOP-r drugs as treatment options for MA dependence; however, partial agonists may be a better option, due to the potential abuse liability associated with full agonists.

[1] Department of Behavioral Neuroscience and Methamphetamine Abuse Research Center, Oregon Health & Science University
[2] Veterans Affairs Medical Center Portland, Oregon.

Funding Support: NIDA T32 DA07262, Department of Veterans Affairs and NIDA P50 DA018165



TUESDAY
MAY 21

poster # 11

Brain cannabinoid system and maternal deprivation: sex-dependent alterations in genetic expression of adolescent rats

V Echeverry-Alzate[1], JA López-Moreno[1], S Peñasco[2], EM Marco[2], AB López-Rodríguez[2], E Giné[3] and MP Viveros[2]

The early neonatal age constitutes a sensitive period for responsiveness to external environmental factors. In this sense, early life maternal deprivation (MD) of rats (24h at postnatal day 9) has been reported to produce behavioral alterations associated with depressive- and psychotic-like symptoms, as well as disturbances in the development of diverse brain areas that affect neurons, glia and synaptic plasticity. During early developmental phases the endocannabinoid system (ECS) affects the expression of key genes for neural development and participates in several important processes such as establishment of correct neuronal connectivity. We have previously shown that induces sex-dependent alterations in the expression of endocannabinoid receptors, endocannabinoid levels and enzymes involved in their synthesis and degradation in developing rats. In the present study we focused on the effects of MD on the genetic expression of the main components of the ECS. We analyzed ECS-related receptors and enzymes in the prefrontal cortex, caudate-putamen, nucleus accumbens, hippocampus, and amygdala of adolescent rats of both sexes. Cnr1 and MgII were the most abundantly expressed genes in the five regions studied, whereas PparχGpr55, Cnr2a and Cnr2b showed the lowest expression. MD induced a general increase of hippocampal gene expression in females and in the prefrontal cortex of males, and additional specific sex-dependent changes in the other brain regions analyzed. Among control non MD animals, sexual dimorphisms were also observed mainly in the prefrontal cortex, with females showing higher gene expression. Present findings indicate a
region- and sex-dependent vulnerability of the ECS to early life stress.

[1] Laboratory of Psychobiology, Department of Psychobiology, Faculty of Psychology
[2] Department of Physiology (Animal Physiology II), Faculty of Biological Sciences
[3] Department of Biochemistry, Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain

Funding Support: Ministerio de Economía y Competitividad (SAF2011-26818, to J.A.L-M.) and Instituto de Salud Carlos III, Redes temáticas de Investigación Cooperativa en salud, RD06/0001/1011 (to J.A.L-M.) and RD06/0001/1013 (to M.P.V.)

TUESDAY
MAY 21

poster # 12

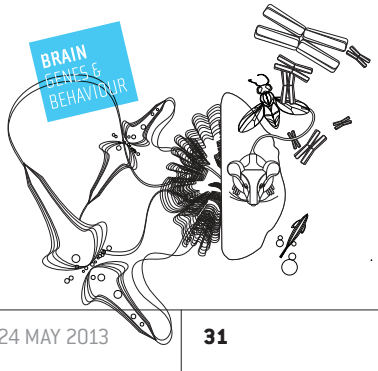
The influences of stress-related genes on HPA axis reactivity in alcoholics and cocaine addicts and their expression in postmortem hippocampus

M.-A.Enoch[1], Z. Zhou[1], D.C. Mash[2], Q. Yuan[1], D. Goldman[1], R. Sinha[3]

This study investigated influences of stress-related genes on HPA axis response to acute stress in addicted individuals and gene expression in hippocampus.
Inpatient alcoholics (AD) (N=51, 8 women), cocaine addicts (CO) (N=48, 20 women) and 57 healthy controls (29 women) were exposed to personalized script-driven stress or neutral imagery while blood cortisol levels were periodically measured. Haplotype tagging SNPs were genotyped across five HPA-axis genes: CRH, CRHBP, CRHR1, NR3C1 and FKBP5. RNA-Seq was used to quantify mRNA transcripts in postmortem hippocampus from eight alcoholics, eight cocaine addicts and eight controls.
All three groups of women and male AD had lower cortisol levels with a greater decline over time compared with male CO and HC in both the stress and neutral conditions. Only male HC and CO showed a cortisol response to stress. The CRH SNP rs6472257 minor allele was associated with increased area under the curve cortisol in the stress, but not the neutral condition in both sexes and all groups ($p=0.007$). This effect was more marked in men. There were similar effects of two other linked SNPs, rs6996265 and rs3176921 ($p < 0.05$). There were no significant results for the other genes. CO showed lower expression of CRH ($p=0.006$) and CRHBP ($p=0.009$) and higher expression of FKBP5 ($p=0.032$). Gene expression in alcoholics did not differ from controls.
We have shown that CO and AD differ in both HPA axis stress response and hippocampal stress-gene expression. The influence of CRH variation on cortisol levels is independent of group and sex.

[1] National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA
[2] University of Miami School of Medicine, Miami, FL, USA
[3] Yale Stress Center, Yale University School of Medicine, New Haven CT USA.

NIH grants: R01-AA013892; PL1-DA024859, PL1-DA024860, P50-DA016556; UL1-DE019586.)



TUESDAY
MAY 21

poster # 13

Hypoactive profiles confer additional risk for developing cognitive decline in transgenic mouse model of Alzheimer's disease

Mohammed FILALI [1] & Serge RIVEST [1]

Several risk factors associated with Alzheimer's disease (AD) have been identified, including health conditions, genetics, and lifestyle. Interventions targeted at some of these risk factors may offer opportunities for developing preventive and ameliorative drug trials. In this study we examined the association between ambulatory activity status and the incidence of cognitive decline in AD-transgenic mice. The Novel Object Recognition (NOR) task was used to assess their baseline cognitive function, and follow-up testing was carried out 6 months later to assess any changes. At baseline (12 months of age), 71% (29 of 41) of mutants showed a hypoactive profile. After 6 months, 78% of animals with the hypoactive profile developed severe cognitive impairment, compared with 18% of those with a mildly active profile (ratio: 4.33). These results confirm the association between the ambulatory activity pattern and cognitive functions, and indicate that hypoactive profile can predict future cognitive decline. These findings might have important implication to identify a target population for early intervention and development of efficient personalized treatment strategy.

[1] Neurobehavioral Phenotyping Platform, Neuroscience Laboratory, Department of Molecular Medicine, Centre Hospitalier Universitaire de Québec Research Center, Laval University, Québec City, QC, Canada G1V 4G2

Electronic address: Mohammed.Filali@crchul.ulaval.ca
Web site: http://genome.ulaval.ca/neurobehavioral

Support: Canadian Institutes in Health Research (CIHR) supported this research

TUESDAY
MAY 21

poster # 14

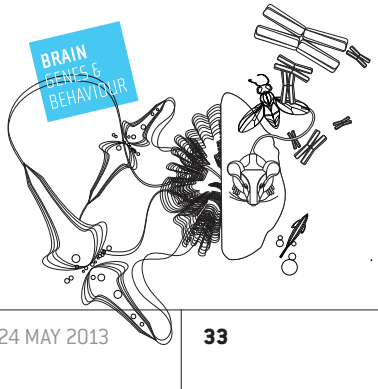
Paradoxical improvements in motor learning in the 3xTg mouse model of Alzheimer's disease

LM Fraser[1], Kurt R. Stover[1], Michelle E. Hicks[1], Kaitlyn M. Gordon[1], J Oore1, RE Brown[1]

The triple transgenic (3xTg) mouse model of Alzheimer's disease (AD) possess three transgenes that lead to the development of amyloid-beta plaques (APPswe, PS1M146V) and neurofibrillary tangles (and tauP301L) (Oddo et al., 2003, Neuron, 39:409-421). Although the neuropathology of these mice has been extensively studied (Sy et al., Neuromethods, 48:469-482), less research has been done to investigate their behaviour, and the majority of behavioural research has focused on cognitive rather than non-cognitive abilities. Two experiments were conducted that investigated motor ability and learning in the 3xTg mouse model. The experiments used a five-day (six trials per day) Rotarod paradigm for male and female 3xTg and control (B6129SF2/J) mice. Experiment 1 used a cross-sectional design investigating mice at 2, 6, 9, 12, and 15 months of age, while Experiment 2 used a longitudinal design to test mice aged 2, 6, 12, and 18 months of age. Paradoxically, both male and female 3xTg mice outperformed controls on all days and at all ages, in both experiments. The 3xTg mice showed superior motor coordination (longer latency to fall), as well as better motor learning (higher learning scores), compared to their age-matched controls. This improved motor performance in 3xTg mice may be related to the background genes of the mice, to the effect of the transgenes on motor function, or to differences in motivation between the strains.

[1] Department of Psychology and Neuroscience, Dalhousie University, Halifax NS, Canada

Funding support:
National Sciences and Engineering Research Council (NSERC), 350 Albert Street, 16th Floor, Ottawa, ON, Canada; Alzheimer's Society of Canada (ASC), 20 Eglinton Avenue West, 16th Floor, Toronto, ON, Canada



TUESDAY
MAY 21

poster # 15

Mice selectively bred for high drinking in the dark exhibit reduced sensitivity to the ataxic and hypnotic effects of ethanol but do not differ in acute functional tolerance capacity relative to progenitor hs/npt mice

Brandon M Fritz[1], Kristy A Cordero[2], Amanda M Barkley-Levenson[2], Pamela Metten[2], John C Crabbe[2], Stephen L Boehm II[1]

Initial sensitivity to ethanol and the capacity to develop acute functional tolerance (AFT) to its adverse effects (e.g. ataxia and hypnosis) may influence the amount of alcohol an individual consumes and may also predict future alcohol use patterns. The goal of the current study was to assess sensitivity and AFT to the ataxic and hypnotic effects of ethanol in the first replicate of mice (HDID-1) selectively bred for high blood ethanol concentrations following limited access to ethanol in the Drinking in the Dark (DID) paradigm. Mice from the HS/Npt progenitor stock were also tested as controls. Ataxia was assessed by the static dowel task which requires animals to balance on a wooden dowel. Ethanol-induced hypnosis was assessed by the method of Ponomarev and Crabbe (2002), using modified restraint tubes to measure the loss of righting reflex (LORR). HDID-1 mice exhibited reduced initial sensitivity to both ethanol-induced ataxia ($p < 0.001$) and hypnosis ($p < 0.05$) as evidenced by significantly higher BEC values at loss of function in both tasks relative to HS/Npt mice. AFT was calculated for both tasks by subtracting the BEC at loss of function from the BEC at recovery. The dowel test yielded no line differences in AFT, but HS/Npt mice developed slightly greater AFT to ethanol-induced LORR than HDID-1 ($p < 0.05$).These results suggest that HDID-1 mice exhibit blunted initial sensitivity to ethanol relative to HS/Npt mice which may influence their subsequent high ethanol intake in the DID paradigm.

[1] Indiana Alcohol Research Center, Department of Psychology Indiana University – Purdue University Indianapolis, Indianapolis, IN 46202 USA
[2] Portland Alcohol Research Center, Department of Behavioral Neuroscience, Oregon Health & Science University, and the VA Medical Center, Portland, Oregon 97239 USA

This work was supported by NIH grants AA016789 (SB) and AA10760, AA13519, and AA020245 (JC), and grants from the Department of Veterans Affairs and the Department of Defense (JC). AMB-L was supported by AA07468, the Achievement Rewards for College Scientists Foundation, and an OHSU Graduate Research Scholar Fellowship

TUESDAY
MAY 21

poster # 16

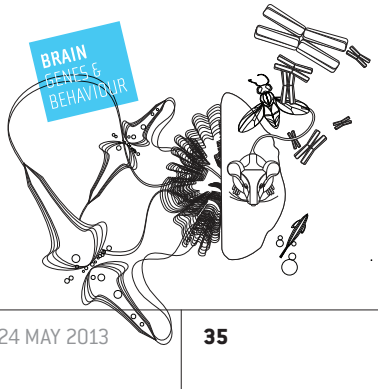
Bdnf expression in response to alcohol consumption and voluntary exercise in adolescent mice

X Gallego[1], RJ Cox1, MA Ehringer[1]

A previous study in our lab showed that adult C57BL/6 mice consume less alcohol when given free access to a running wheel, suggesting that these behaviors may share a common neuronal reward pathway. It is known that significant neurodegeneration occurs in the hippocampus of both animals and humans as a result of prolonged alcohol consumption. In contrast exercise increases neurogenesis in the dentate gyrus of the hippocampus in mice. One protein known to be involved in neurogenesis is brain-derived neurotrophic factor, or BDNF. The contrasting effects of running and alcohol on neurogenesis suggest that BDNF may play a key role in modulating these behaviors. To explore this possibility, we aim to better understand the relation between voluntary exercise and alcohol consumption by analyzing Bdnf mRNA levels in the hippocampus of adolescent mice given free access to a running wheel and alcohol. As in our previous study of adult C57BL/6 mice, our study demonstrates that adolescent mice voluntarily consume less alcohol when given access to a running wheel. In addition, our results show an increase in Bdnf mRNA expression in mice that were exposed to voluntary exercise. However we did not see any differences in the expression of Bdnf mRNA when mice were exposed to alcohol. Interestingly, the effects of voluntary exercise on Bdnf mRNA expression were abolished when mice were simultaneously given free access to a running wheel and alcohol. Although there is a clear interaction between the effects of voluntary exercise and alcohol consumption regarding Bdnf mRNA expression in hippocampus, it is unclear whether BDNF is involved in the decreased alcohol consumption seen in mice exposed to exercise. Further studies are needed in order to elucidate the exact mechanism involved in modulating these behaviors.

[1] Institute for Behavioral Genetics and Department of Integrative Physiology, University of Colorado, Boulder, CO

Funding Support: NIH grant R01 AA017889 (MAE)



TUESDAY
MAY 21

poster # 17

Developmentally-induced hypothyroidism impairs spatial memory, alters the expression of Egr-1 and Arc genes and the sensitivity to cannabinoid agonists in the hippocampus.

Giné E[1,2], Echeverry-Alzate V[3], López-Moreno JA[3], López- Jimenez A[3], Torres-Romero D[2], Buhler K-M[3], Perez-Castillo A[4,5], Santos A[2].

Thyroid hormones play a critical role in the brain development. Hypothyroidism has been associated with morphological, electrophysiological and biochemical alterations in the hippocampus, which are linked to cognitive deficits. Noteworthy evidences demonstrate that the endocannabinoid system contributes in the regulation of cognitive tasks as memory and spatial learning. Here, we aimed to investigate the effect of Developmentally-induced hypothyroidism in adult Wistar rats. For this, we focus on spatial memory, assessed using the Morris Water Maze; and on the biochemical effects of cannabinoid receptor agonists in hippocampus, as determined by their effects on CREB phosphorylation and Egr-1, Arc, c-fos and c-jun gene expression.
We found that spatial learning and basal hippocampal expression of early genes decreased in Developmentally-induced hypothyroidism compared with control rats. Low doses of the cannabinoid receptor agonists WIN 55,212-2 or HU-210, which were ineffective in control rats, altered the spatial learning on hypothyroidism rats and increased their biochemical and genetics responses. Negative effects on spatial learning as well as on biochemical and genetics responses were blocked by the cannabinoid receptor antagonist AM-251, suggesting the implication of the cannabinoid receptor type 1 (CB1) in the increased responses. Also, we found that spatial learning and alterations in gene expression were not explained by a change in the CB1 receptor content. Although thyroid hormones treatment in hypothyroid rats normalized the cannabinoid-induced reduction in spatial learning and genetic expression, it did not correct the low basal level of the spatial learning and the early gene transcripts of these hypothyroid rats. All these data suggest that hippocampal deregulation of early genes expression and the endocannabinoid system could play an important role in basal cognitive deficits of hypothyroid rats.

[1] Department of Cellular Biology, Faculty of Medicine, University Complutense of Madrid. Madrid, Spain
[2] Department of Biochemistry and Molecular Biology, Faculty of Medicine, University Complutense of Madrid. Madrid, Spain
[3] Department of Psychobiology, Faculty of Psychology, University Complutense of Madrid. Madrid Spain
[4] Instituto de Investigaciones Biomédicas, Consejo Superior de Investigaciones Científicas, UAM, Spain.
[5] Centro de Investigaciones Biomédicas en Red sobre Enfermedades Neurodegenerativas, CIBERNED, Madrid, Spain.

This work was supported by the Ministerio de Educación y Ciencia SAF2007-62811 and SAF2010-16365 (to A.P.-C.), SAF2008-03763 and SAF2011-26818 (to JA.L.-M.), Fondo de Investigación Sanitaria (Red de Trastornos Adictivos, FEDER, RD06/0001/0011) (to J.A.L.-M.), and Grupo de Investigación UCM (Grupo 940157) (to JA.L.-M.). CIBERNED is funded by the Instituto de Salud Carlos III

TUESDAY
MAY 21

poster # 18

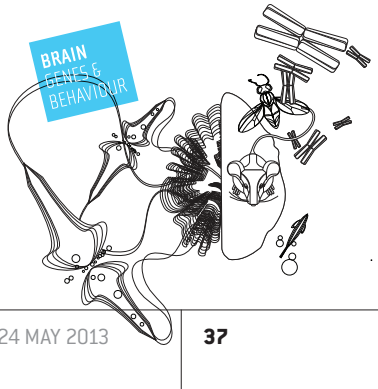
Pellet eating behavior in C57BL/6J, DBA/2J, and hybrid mice

Joseph Gyekis[1] and David Blizard[1]

Non-deprived C57BL/6J (B6) and DBA/2J (D2) mice show marked differences in consumption of 20 mg Noyes pellets provided in a feeding cup during the early hours of the dark cycle. Mice of the D2 strain rapidly consume pellets within a 20 min period, while B6 mice consume the pellets at a much slower rate. The same strain difference is evident in similarly sized pieces of crushed maintenance chow and in mice that have habituated to the presence of the dish in their cages. B6D2F1 hybrids show a phenotype approximately midway between the parental strains. Advanced intercross mice derived from these two strains show a broad variability in the phenotype. Ongoing efforts, will map any quantitative trait loci associated with rate of pellet consumption in 400 F9 to F13 B6D2 advanced intercross mice genotyped at approximately 20,000 loci.

[1] Department of Biobehavioral Health, Pennsylvania State University, University Park, PA, 16802

Support: National Institute of Arthritis and Musculoskeletal and Skin Diseases R01, AR056280, USA



TUESDAY
MAY 21

poster # 19

Norepinephrine and stress axis activation may influence aversive effects of methamphetamine.

*J. H. Harkness[2, 3], t. J. Phillips[1, 2,3]

Methamphetamine (MA) High Drinking (MAHDR) mice are sensitive to rewarding effects of MA, but insensitive to aversive effects. The opposite has been shown in Methamphetamine Low Drinking (MALDR) mice. Norepinephrine transporters (NET), but not other monoamine transporters, appear to mediate cocaine-induced taste aversion. MA induces norepinephrine (NE) release, and NE activity may stimulate hypothalamic-pituitary-adrenal (HPA) axis activity. We hypothesized that differences in NET activity may underlie MA drinking (MADR) line differences. To measure a NET-mediated response, a conditioned taste aversion (CTA) procedure with a novel NaCl tastant was used to examine sensitivity to CTA induced by the NET blocker, nisoxetine in MADR mice. NET blockade alone was sufficient to induce CTA and there was a tendency for the aversive effect to occur more rapidly in MALDR than MAHDR mice. In a second study, we hypothesized that MA would increase plasma CORT levels to a greater extent in MALDR than MAHDR mice. Compared to MAHDR, MALDR mice had higher plasma corticosterone levels 30 minutes after administration of 2 mg/kg MA. These results, in addition to previously reported differences in NET and SERT expression, suggest that a difference in NET activity between the lines may play a role in some of their differential responses to MA, including MA drinking and MA-induced CTA. Further, a stronger HPA response may be responsible for heightened aversive effects of MA in the MALDR line. Additional studies will examine SERT blocker-induced CTA, the ACTH response to MA, and whether monoamine transporter blockers substitute for MA in CTA.

[1] Veterans Affairs Med. Ctr., Portland, OR
[2] Behavioral Neurosci.
[3] Methamphetamine Abuse Res. Ctr., Oregon Hlth. & Sci. Univ., Portland, OR

Funding: The Department of Veterans Affairs, NIH NIDA P50DA018165 and T32DA07262

TUESDAY
MAY 21

poster # 20

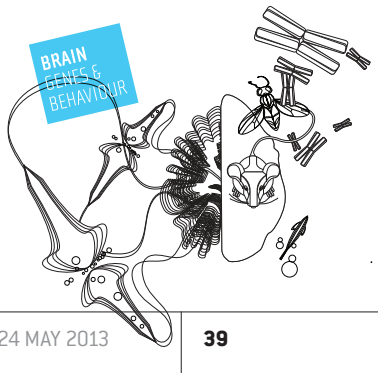
Alcohol dependence: leveraging intermediate phenotypes to uncover epigenetic biomarkers

KE Hutchison, N Harlaar, AD Bryan

While the field has been focused on genetic research for some time, research designed to identify epigenetic biomarkers associated with course of addiction is relatively nascent. The etiology of alcohol dependence is related to changes in the neuronal systems involved in the anticipation of reward and executive control. Epigenetic variations that are associated with individual differences in these mechanisms may be important in terms of predicting the course of dependence as well as treatment outcomes. We recently developed an approach that leverages intermediate phenotypes to link epigenetic variation to changes in neuronal function and clinical measures. In a recent study, an exploratory epigenome wide analysis identified several promising DNA methylation sites that were associated with measures of alcohol dependence. These methylation sites are near the ALDH1A2, DRD2, and HTR3D genes. Additional analyses indicated that methylation at the ALDH1A2 CpG site is associated with the amount of time necessary to reach a target breath alcohol level during an ethanol infusion and the subjective experience of intoxication, suggesting that this methylation site may be associated with metabolism of ethanol. CpG sites near the DRD2 and HTR3D genes are more strongly associated with responses to alcohol cues and functional connectivity in control networks in the brain. The results suggest that methylation of CpGs in the promoter regions of these genes may play a role in the etiology of alcohol dependence.

[1] Department of Psychology & Neuroscience, University of Colorado Boulder, Boulder, Colorado, USA

National Institutes of Health, NIAAA R01 AA015968-01A2, NIAAA R01AA012238



TUESDAY
MAY 21

poster # 21

Genetic association between brain and behavioural measures in Heterogeneous Stock mice

MU Janecka[1], MJ Parsons[2], L Liu[1], R Smith[1], JL Paya-Cano[1], C Fernandes[1], LC Schalkwyk[1]

The success of the search for quantitative trait loci (QTLs) remains mixed, despite considerable resource investment. Their complicated genetic architecture still escapes our investigation, with phenomena like pleiotropy, polygeny, epistasis and gene-environment interaction not yet dissected at the molecular level.

Our project aimed to investigate the genetic basis for brain weights, activity, anxiety and cognition in a sample of adult, male Heterogeneous Stock (HS) mice. We used an approach of single nucleotide polymorphism (SNP) hunting in candidate genes, focusing on the genes involved in the most prominent neurotransmitter pathways (serotonin, glutamate, gamma-aminobutyric acid (GABA) and dopamine) and transcription factors. We hypothesised that polymorphisms in these would associate with changes in behaviour and/or brain weights in adult mice, indicating potential genetic and/or neuroanatomical substrates of behaviour in mouse.

Our analysis suggested several genes significantly associated with behavioural and brain measures assessed in the HS mice. Interestingly, the loci mediating alterations in these two domains differed. Our findings will be discussed in the light of the low numbers of minor allele homozygotes in the HS, and how other mouse tools such as the Diversity Outbred and Collaborative Cross stocks can help overcome this issue.

[1] Social, Genetic and Developmental Psychiatry MRC Centre, Institute of Psychiatry, King's College London, United Kingdom
[2] Mammalian Genetics Unit, Medical Research Council – Harwell Oxfordshire, United Kingdom.

Funding for this work was provided by the Medical Research Council (G0000170) Career Establishment award to LC Schalkwyk

TUESDAY
MAY 21

poster # 22

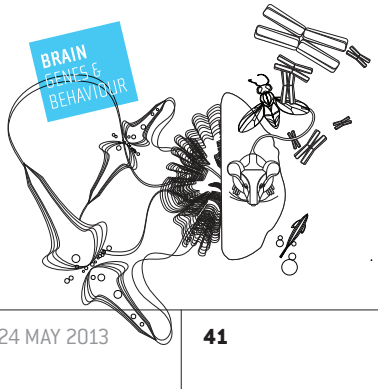
Prenatal sex differences in the human brain before and after sexual maturation of the gonads

MM Johansson[1], E Darj[2], D skuse[3], L Feuk[4] and E Jazin[1]

In 2009, we reported that eleven Y-linked genes are highly expressed in all regions of the male brain in mid-gestation human embryos (12-16 weeks) (Reinius B. and Jazin E. Prenatal sex differences in the human brain. Mol Psychiatry 2009 14:987-9). The function of these genes in the brain during development is not known. We have now extended these investigations and analyzed human embryos collected earlier, between 7-11 weeks of gestation, before (and immediately after) the primordial sex organs differentiate into testicles or ovaries, and start to produce oestrogens or androgens. The Swedish ethical committee approved all experiments, all tissues were immediately fixed in 4% formaldehyde and/or frozen, and no cells remained alive. Results will be presented on expression levels, tissue and cellular distribution of genes encoded by the Y chromosome as well as X-encoded genes known to escape X inactivation. Furthermore, some selected samples were subject to RNA-sequencing designed to evaluate similarities and differences of sex bias in gene expression before and after sexual maturation of the human gonads.

[1] Department of Organismal Biology, EBC, Uppsala University
[2] Institution of Women's and Children's Health, Uppsala University
[3] Institute of Child Health, University College London
[4] Department of Immunology, Genetics and Pathology, Rudbeck Laboratory and Science for Life Laboratory, Uppsala University

Funding support: Swedish National Science Foundation (Vetenskapsradet), Project grant 2011-3471



TUESDAY
MAY 21

poster # 23

R(+)- baclofen attenuates ethanol intake in High Alcohol Preferring Line 1 mice

CR Kasten [1], SL Boehm II [1,2]

High Alcohol Preferring (HAP) mice are selectively bred for consumption of 10% ethanol. HAP mice reach pharmacologically relevant ethanol intakes during 24-hour two-bottle choice drinking, making them a viable model for screening potential alcohol use disorder (AUD) treatments. The GABAB agonist baclofen has been looked at extensively for treatment of AUDs. In pre-clinical consumption studies, baclofen has been shown to reduce and increase overall ethanol consumption. In Experiment 1, HAPI mice received 20 days of 24-hour two-bottle choice exposure to 10% ethanol. At the beginning of the dark cycle on Day 19 all mice received a saline habituation injection. On Day 20 mice received an injection of 0, 1, 3, or 10 mg baclofen. Injections on Days 19 and 20 took place at the beginning of the dark cycle. Consumption was recorded for a half hour. The 10mg dose of baclofen significantly reduced ethanol consumption ($p<.05$). In Experiment 2, HAP1 mice were given 16 days of 24-hour free-choice access to either 0.32% saccharin or 10% ethanol. On Day 15 a saline habituation injection was given. On Day 16 a 10mg dose of baclofen was given. Both injections took place immediately prior to the dark cycle and consumption was recorded for three hours. There was a trend towards a main effect of injection in the saccharin group, with baclofen reducing drinking ($p = .05$). In the ethanol group there was an interaction of Time*Injection type, with baclofen reducing drinking across 3rd and 4th time points ($p<.05$). These results further implicate a role for GABAB receptors in treating AUDs.

[1] Department of Psychology, Indiana University Purdue University – Indianapolis, Indianapolis, IN
[2] Alcohol Research Center, Indianapolis, IN

Funding Support: NIAAA grant #AA016789 and the Indiana Alcohol Research Center (AA007611)

TUESDAY
MAY 21

poster # 24

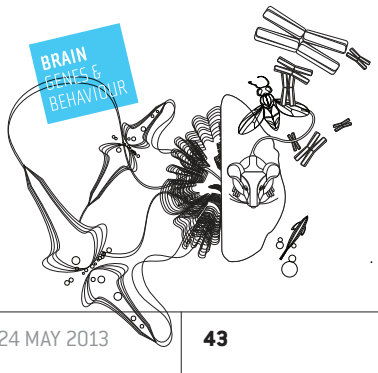
Food intake and ethanol preference are genetically distinct traits in Drosophila melanogaster

CL Kliethermes[1], WR Szmanda[1] and KE Hogan[1]

Drugs of abuse act on neural circuits that are believed to have evolved to motivate animals towards food and other natural reinforcers, and most current theories of the etiology of drug abuse and dependence are based either explicitly or tacitly on this premise. Like mammals, insects have a long evolutionary relationship with drugs of abuse, including the psychoactive pesticides nicotine and cocaine, and the fruit fly Drosophila melanogaster is well known to use ethanol-containing food as a major source of nutrition. The current experiments used a subset of recombinant inbred (RI) fly lines from the Drosophila Genetic Reference Panel to test whether common genes might underlie food intake and ethanol preference. Food intake was quantified by measuring the amount of dyed food consumed in a 30 minute session, and ethanol preference was measured using the olfactory trap assay. The RI lines differed markedly in their responses, with close to half of the total variation in each assay attributable to genetics in each assay. However, no significant genetic correlation was found between food intake and ethanol preference, indicating that common genes do not underlie these behaviors. We are currently testing this panel of flies in more naturalistic and quantitative models of food and ethanol preference, as well as beginning functional studies to characterize the role of individual neural circuits in these behavioral assays. These experiments will identify genes and neural circuits that function independently in each assay, as well as those that might coregulate food and ethanol intake.

[1]Department of Psychology and Program in Neuroscience, Drake University, Des Moines IA USA

Funding Support: These experiments were supported by funds from Drake University



TUESDAY
MAY 21

poster # 25

Impact of social context on behaviour of C57BL/6 and DBA/2 female mice

N. Kulesskaya[1], H. Rauvala[1], V. Voikar[1]

Behavioural phenotyping of genetically modified mice is an effective tool to explore mechanism underlying neurological and psychiatric disorders. Social interaction could affect behavioural traits and is suggested to be implemented as a treatment approach in some psychiatric disorders. Nevertheless, the impact of social factors to different aspects of other behavioural paradigms in mice is purely understood. We used C57BL/6 and DBA/2 female mice for testing how the animals with different behavioural strategies could affect each other when they are housed together in mixed groups. Standard behavioural tests and assessment in automated IntelliCage system were applied to animals housed in mixed (C57BL/6 plus DBA/2) or separated (C57BL/6 or DBA/2 only) groups. Previously it has been shown that DBA/2 mice are more anxious and display impaired learning in comparison with C57BL/6 mice. We found that DBA/2 mice avoid social contact, loose in social competition with C57BL/6 in tube test and show impaired nest building. Social environment had dramatic effect on the behaviour in socially active C57BL/6 mice but not in DBA/2 mice. The C57BL/6 mice housed in mixed group demonstrated increased locomotor activity and decreased preference to saccharine consumption in IntelliCage, impaired learning in patrolling task, more anxious behaviour in the light-dark test and loose of social competence in social tube test in comparison with C57BL/6 mice housed separately. Our results demonstrate impact of social factors on behavioural phenotype.
This impact depends on the genetic background and needs to be considered in studies where group housed animals of different strains are used.

[1] Neuroscience Center, University of Helsinki, Helsinki, Finland

Funding Support: Biocenter Finland

TUESDAY
MAY 21

poster # 26

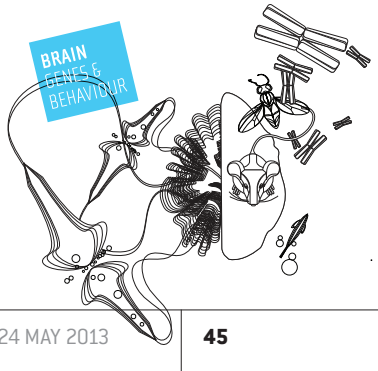
Amygdala first wave transcriptome in serotonin transporter knockout mice following an acute stressor

Christa Hohoff[1], Ali Gorji[2], Sylvia Kaiser[3,4], Edith Willscher[5], Eberhard Korsching[6], Oliver Ambrée[1], Volker Arolt[1,4], Klaus-Peter Lesch[7], Norbert Sachser[3,4], Jürgen Deckert[7], Lars Lewejohann[3,4]

The most prominent brain region evaluating the significance of external stimuli immediately after their onset is the amygdala. Stimuli evaluated as being stressful actuate a number of physiological processes as an immediate stress response. Variation in the serotonin transporter gene has been associated with increased anxiety- and depression-like behavior, altered stress reactivity and adaptation, and pathophysiology of stress-related disorders.
Here the instant reactions to an acute stressor were measured in a serotonin transporter knockout mouse model. Genome-wide gene expression changes in the amygdala were measured after the mice were subjected to control condition or to an acute stressor. The dissection of amygdalae and stabilization of RNA was conducted within nine minutes after the onset of the stressor. This extremely short protocol allowed for analysis of first wave primary response genes, typically induced within five to ten minutes of stimulation. RNA profiling revealed a largely new set of differentially expressed primary response genes that differed distinctly between wild-type and knockout mice. Consequently, functional categorization and pathway analysis indicated genes related to neuroplasticity and adaptation in wild-types whereas knockouts were characterized by impaired plasticity and genes more related to chronic stress and pathophysiology. Our study disclosed different coping styles dependent on serotonin transporter genotype even directly after the onset of stress, accentuating the role of the serotonergic system in processing stressors and threat in the amygdala. Moreover, several of the first wave primary response genes that we found might provide promising targets for future therapeutic interventions of stress-related disorders also in humans.

[1] Department of Psychiatry, University of Muenster, Muenster, Germany
[2] Institute of Neurophysiology, University of Muenster, Muenster, Germany
[3] Department of Behavioural Biology, University of Muenster, Muenster, Germany
[4] Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, University of Muenster, Germany
[5] Integrated Functional Genomics (IFG), Core Unit of the Interdisciplinary Centre of Clinical Research (IZKF) Muenster, Muenster, Germany
[6] Institute of Bioinformatics, University of Muenster, Muenster, Germany
[7] Department of Psychiatry, University of Wuerzburg, Wuerzburg, Germany

Funding Support: This study was supported by the fund “Innovative Medical Research” of the University of Muenster Medical School to CH (HO 2 2 05 09) and by a grant from the German Research Foundation (DFG) to NS and KPL (SFB/TRR58, Project A1)



TUESDAY
MAY 21

poster # 27

The activation of EphA4 signaling regulates the proteolysis of amyloid precursor protein through a Lyn-mediated pathway

Yung-Feng Liao[1,2,3], Wei-Bin Lai[1,2], Bo-Jeng Wang[2,3]

Alzheimer's disease is the most common dementia afflicting the elderly in the modern society. This disease is a result of the neurotoxicity elicited by abnormal amyloid-β (Aβ) protein aggregates. Aβ is generated by the γ-secretase-catalyzed proteolysis of amyloid precursor protein (APP) C-terminal fragment (APP-βCTF) that is released by the b-secretase cleavage of APP. Recent evidence suggests γ-secreatse's substrate βCTF and its metabolite APP intracellular domain (AICD) could exert harmful effects on cells, suggesting that the proteolytic products of APP, including Aβ, βCTF, and AICD, could play a pivotal role in neuronal viability. Here, we demonstrated that ligand-activated EphA4 signaling could govern the proteostasis of βCTF, AICD, and Aβ independent of γ-secretase activity. The inhibition of EphA4 by Dasatinib, a receptor tyrosine kinase inhibitor, effectively suppressed the EphA4-induced accumulation of βCTF and AICD. This EphA4-elicited accumulation of βCTF and AICD was mediated by a Lyn-dependent pathway whose activation could in turn phosphorylate EphA4 to constitute a positive feedback in governing the proteostasis of βCTF and AICD. Furthermore, EphA4 signaling could regulate the ubiquitin-proteasome system to control the proteolysis of βCTF and AICD. In conclusion, our data delineate an EphA4-Lyn pathway that is essential for the metabolism of APP and its proteolytic derivatives, providing novel pharmacological targets for the development of anti-Aβ therapeutics for AD.

[1] Institute of Life Science, National Defense Medical Center, Taipei, Taiwan
[2] Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan
[3] Institute of Zoology, National Taiwan University, Taipei, Taiwan.

TUESDAY
MAY 21

poster # 28

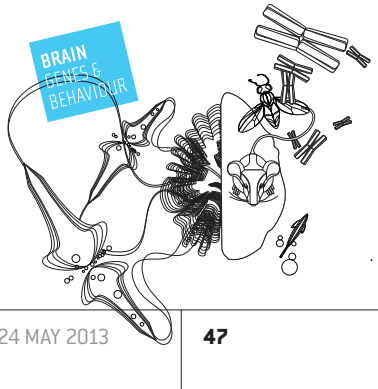
Single Nucleotide Polymorphisms Associated with Drug-Related Phenotypes: the Past 12 Years

J. A. López-Moreno[1], V. Echeverry-Alzate[1], E. Giné2, K.M. Bühler[1]

Since the human genome sequence was published, the number of studies investigating the association of genetic variants with diseases and multiple human phenotypes has increased dramatically. In this work, we summarize only those studies published since 2000 that have found significant associations between alcohol-, smoking-, cannabis- and cocaine–related phenotypes and Single Nucleotide Polymorphisms (SNPs). Alcohol- and smoking–related phenotypes have been associated with more than seven hundred and near five hundred SNPs respectively. However, in both cases, only a few SNPs and their respective genes (≈10%) have been associated in numerous studies with a drug-related phenotype. Receptor and enzyme SNPs in dopaminergic, GABAergic and cholinergic neurons, as well as in liver enzymes, explain the majority of the associations found. We provide an update for the current challenge for developing better pharmacological treatments, biomarkers and prevention strategies for substance abuse.

[1] Dept. of Psychobiology, Faculty of Psychology, Complutense University of Madrid, Spain
[2] Dept. of Cellular Biology, Faculty of Medicine, Complutense University of Madrid, Spain

Support: Fondo de Investigación Sanitaria (Red de Trastornos Adictivos, FEDER, RD06/0001/0011), Ministerio de Economía y Competitividad (SAF2011-26818), Agencia Antidroga de la Comunidad de Madrid (Art.83), and The European Foundation for Alcohol Research (EA 12 21 to J.A.L.M.).



TUESDAY
MAY 21

poster # 29

Pharmacological assessment of a selectively bred hyperactive mouse line to model ADHD

P Majdak[1], PJ Bucko[1], AL Holloway[1], A Kobeissi[1], JM Ossyra[1], TK Bhattacharya[1], JS Rhodes[1]

Attention deficit-hyperactivity disorder (ADHD) is a widely recognized behavioral disorder characterized by hyperactivity, inattention and impulsivity, and ameliorated by ADHD medication including d-amphetamine (Adderall). Recent work from our lab has shown that daily, long-term administration of clinically relevant doses of amphetamine to inbred C57BL/6J mice results in a dose-dependent enhancement of hippocampal neurogenesis. However, in order to most accurately model a multifactorial disorder such as ADHD, mice selectively bred for home cage hyperactivity were used. Following an 11 generation selective breeding experiment, these mice display a key ADHD-like characteristic of increased levels of home cage locomotor activity. The purpose of this experiment was to 1) evaluate our selectively bred hyperactive mice for predictive validity in their locomotor response to daily d-amphetamine, 2) determine whether clinically relevant doses of amphetamine in this selectively bred strain impact cognitive performance, and 3) evaluate the neurogenic impact of both baseline home cage hyperactivity and clinically relevant amphetamine doses. Beginning in early adolescence through adulthood, 80 selectively bred male and female mice were administered twice daily i.p. injections of vehicle, 0.25, 0.5 or 2 mg/kg d-amphetamine. Mice were also given 10 daily i.p. injections of 50 mg/kg BrdU to label dividing cells. Mice were monitored by video tracking for changes in locomotor activity on drug administration days 16-18 and 40-42. Following administration, mice were tested on the Morris water maze on drug administration days 43-47. Locomotor activity, Morris water maze learning, and BrdU+ hippocampal cells were the primary measures evaluated in this study.

[1] Department of Psychology, The Beckman Institute, 405 N Mathews Ave, University of Illinois at Urbana-Champaign, Urbana, IL, 61801, USA

TUESDAY
MAY 21

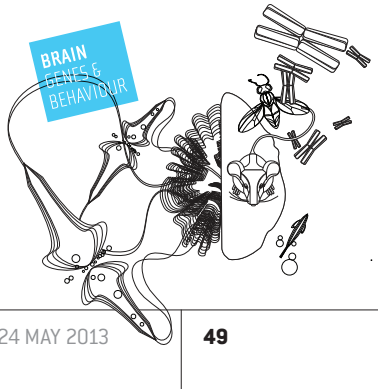
poster # 30

Molecular mechanisms of d-cycloserine in fear extinction: insights from rna sequencing

Malan-Müller S[1], Fairbairn L[1], Jalali M[2], Oakeley EJ[4], Gamieldien J[2], Kidd M[3], Seedat S[1], Hemmings SMJ[1]

Introduction Posttraumatic stress disorder (PTSD) is a severe, chronic and debilitating psychiatric disorder that can occur after a traumatic event. D-cycloserine (DCS), a partial N-methyl-D-aspartate (NMDA) receptor agonist, has been found to be effective in facilitating fear extinction in both animal and human studies of anxiety. However, the precise mechanism whereby DCS facilitates fear extinction is unknown. The aim of this study was to elucidate the molecular mechanism of action of DCS in facilitating fear extinction in a rat model of PTSD.
Methods Adult Sprague-Dawley rats were grouped into four experimental groups (30 rats/group), with saline or DCS infused intrahippocampally. Animals were subjected to behavioural tests to determine which displayed anxiety-like behaviour. RNA was extracted from the left dorsal hippocampi (LDH) and was used for RNA seq analysis. Differentially expressed genes between different treatment groups were identified using bioinformatics analyses. Suitability of qPCR as verification analysis of sequencing data was also investigated in cDNA from brain and blood samples.
Results The focus experimental groups were fear + saline maladapted (FSM) vs fear + DCS well adapted (FDW) groups in order to identify DCS induced fear extinction gene expression changes. 108 genes were significantly downregulated in the FDW group compared to the FSM group, 32 genes were predicted to be biologically significant based on their function. Integrative biomolecular interaction network analyses revealed that subsets of these differentially expressed genes are common between memory disorders, nervous system diseases, metabolic disorders as well as substance- and alcohol-related disorders; these included Trh, Mmp9, Mt2a, Clec7a, Il1rn, Npy, Spp1 and Cybb. Biological functions of differentially expressed genes ranged from negative regulation of glutamate secretion, response to drug or stress, behaviour and locomotion. Relative expression analyses with qPCR detected three differentially expressed genes (Cybb, Mt2a and Il1rn) from a panel of eight selected genes (chosen from sequencing results). qPCR analyses were also able to detect differential expression of the matrix metallopeptidase 9 (Mmp9) gene in the blood cDNA.
Conclusions Differential gene expression analyses in this PTSD animal model enabled us to identify genes, networks and pathways that might explain how DCS facilitates fear extinction. Furthermore, differentially expressed genes that were common in different diseases might help to explain the co-morbidity described for some of these diseases. Identifying the molecular underpinnings of fear extinction might bring us closer to understanding and effectively treating PTSD.

[1] Stellenbosch University, Department of Psychiatry, Cape Town, South Africa
[2] University of the Western Cape, South African National Bioinformatics Institute, Cape Town
[3] Stellenbosch University, Centre for Statistical Consultation, Stellenbosch, South Africa
[4] Novartis Institutes for BioMedical Research, Biomarker Development - Human Genetics and Genomics, Genome Technologies, Basel, Switzerland



TUESDAY
MAY 21

poster # 31

Behavioral and transcriptomic sex differences, despite identical genetics, in a rat model of depression

N.S. Mehta[1], H. Chen[2], L. Wang[1,3], E.E. Redei[1]

Major depressive disorder (MDD) is a common, debilitating illness with high prevalence of co-morbid anxiety. The incidence of depression, and of co-morbid anxiety is much higher in women than in men. These gender biases appear after puberty and their etiology is mostly unknown. Using bi-directional selective breeding from the Wistar Kyoto (WKY) rat strain, an accepted model of adult and adolescent depression, we have generated two fully inbred sub-strains now at their 29th generation. The adult WKY More Immobile (WMI) rats of both sexes consistently show increased depression-like behavior in the forced swim test when compared to the control WKY Less Immobile (WLI) strain. Whole genome sequencing determined 412 exonic sequence variations between these two inbred strains, of which 243 also differed between WMI and the reference genome. By the 24th generation, anxiety-like behaviors also segregated between the strains in males. Specifically, while adult male WMIs are not anxious, WLIs display high anxiety-like behaviors. In contrast, both WMI and WLI females show high anxiety-like behaviors in adulthood. The behavioral profile of male WMIs are consistent from pre- to post-puberty, while that of the female WMIs' appears only after puberty. These sex- and age-specific behavioral patterns are paralleled by hippocampal gene expression differences. Thus, the contribution of specific genes, and/or the influence of the gonadal hormonal environment to depression- and anxiety-like behaviors may differ between male and female WMIs, resulting in their distinct behavioral and transcriptomic profiles despite shared sequences of the somatic chromosomes.

[1] Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA
[2] Department of Pharmacology, University of Tennessee Health Science Center, Memphis, Tennessee, USA
[3] Department of Radiology, Northwestern University, Chicago, Illinois, USA

Support: Davee Foundation

TUESDAY
MAY 21

poster # 32

Cholinergic-associated genes: A principal components analysis of gene expression patterns

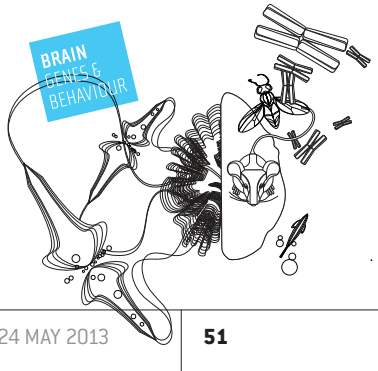
WE Melroy[1,2], M Simonson[1,3], MB McQueen[2], MA Ehringer[1,2]

Upon chronic exposure to nicotine, nicotinic acetylcholine receptors (nAChRs) are known to undergo upregulation of receptor numbers (Schwartz & Kellar 1983; Marks 1983; Benwell 1988). However, upregulation of receptor number is not due to an increase in mRNA of nAChR genes (Marks 1992). This phenomenon has lead to various theories on how nAChRs undergo upregulation, including increased receptor trafficking (Darsow 2005), decreased nAChR subunit degradation (Rezvani 2007, 2009), increased nAChR subunit maturation and folding (Harkness & Millar 2002; Nashmi 2003; Sallette 2005), and increased translation and 2nd messenger signaling (Gopalakrishnan 1997). Through manual curation of primary literature and in discussion with experts in the nAChR field, we have developed a list of 96 gene products known to interact with nAChRs and through their interaction may promote increased surface expression.

The goal of the current project is to characterize the patterns of expression for our list of cholinergic-related genes in the human brain. Using RNAseq data available from the Allen Brain Atlas (http://www.brain-map.org) and a principle components approach, we are investigating where these genes show similar coordinated patterns of expression throughout different brain regions. Using samples from the striatum, amygdala, and hippocampus we have analyzed expression patterns of our targeted genes in 7 adults. Our analyses revealed particular genes (e.g. YWHAQ, NLGN1, and CANX) whose expression profiles cluster together. We plan to integrate these analyses with ongoing work examining these same genes using existing Genome-Wide Association data to provide improved understanding of how they may be involved in smoking behaviors.

[1] Institute for Behavioral Genetics, University of Colorado, Boulder, CO, USA
[2] Department of Integrative Physiology, University of Colorado, Boulder, CO, USA
[3] Department of Psychology and Neuroscience, University of Colorado, Boulder, CO, USA

This work supported by AA017889 and DA017637.



TUESDAY
MAY 21

poster # 33

Social Communication Deficits in Synapsin II Knockout Mice

C Michetti [1], M Morini [2], B Greco [2], F Benfenati [2*], ML Scattoni [1*]

Autism spectrum disorders (ASD) are heterogeneous neurodevelopmental disorders characterized by deficits in social interaction, social communication and repetitive behaviors. Epilepsy is often observed in autistic children and, conversely, several forms of epilepsy display ASD. Given the high comorbidity between ASD and epilepsy, the possibility of a common genetic basis for both diseases has been proposed. Synapsins (Syns) are a family of synaptic vesicle phosphoproteins encoded by the SynI, SynII and SynIII genes. The Syn gene family is a good candidate for the synaptic epilepsy/ASD pathway, as Syns regulate synaptic transmission and plasticity with distinct roles in excitatory and inhibitory neurons.
Aim of our study was to analyze whether deletion of SynII gene in mice causes social communication deficits at adulthood. Analysis of social and vocal repertoires revealed a clear social investigation deficit in Syn II-/- male mice associated with an absence of emission of ultrasonic vocalizations during male-female social interaction. Olfactory investigation allows the mouse to gather biologically meaningful information on the identity of a conspecific, such as social status and sex. There is compelling evidence that ultrasonic vocalizations in this context not only serve to establish or to maintain social contact but are predictors of mating opportunities and are associated with reward expectations. The social communication deficit observed in Syn II-/- mice supports the view that this gene is also involved in the expression of social behavioral traits associated with ASD and suggests as this mutant mouse line represents a good experimental model to study ASD with epilepsy.

[1] Department of Neurotoxicology and Neuroendocrinology, Istituto Superiore di Sanità, Via Regina Elena 299, 00161 Rome, Italy
[2] Department of Neuroscience and Brain Technologies, Istituto Italiano di Tecnologia, Via Morego 30, 16163 Genoa, Italy
[*] These authors contributed equally

Supported by the Italian Ministry of Health Grant (GR3), Young Researcher 2008, "Non-Invasive tools for early detection of Autism Spectrum Disorders" (MLS), Telethon – Italy (GGP09134) and Compagnia di San Paolo (FB)

TUESDAY
MAY 21

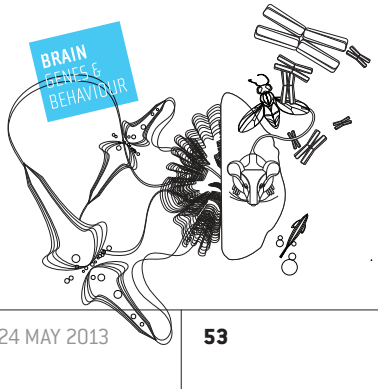
poster # 34

Genetic dissection of behavioral and metabolic phenotypes using a test cross between C57BL/6 substrains

Megan K. Mulligan[1], A.L. Adler[1], A. Pandey[1], S. Roy[1], J. Ingels[1], L. Lu[1], R.W. Williams[1]

We have generated a genetic test cross with low genomic diversity but moderate phenotypic diversity by using C57BL/6J (B6J) and C57BL/6NJ (B6NJ) as parental strains. These substrains have been separated since the 1950s and are known to differ at ∝ 10,000 SNPs and 22,000 small indels and show marked differences for a surprisingly large number of traits. To evaluate the function of these variants we generated an F2 intercross (∝200 cases) and phenotyped the progeny for eight traits shown previously to differ between parental strains—alcohol preference, anxiety, motor coordination, activity in a novel environment, acoustic startle and PPI, pain sensitivity, and glucose and insulin tolerance. To genotype progeny, we designed a custom Fluidigm SNP genotyping array with 84 markers spaced ∝30 Mb apart. There is significant variation among F2 progeny and parental strains for alcohol preference, acoustic startle and pre-pulse inhibition, activity, anxiety, body weight, and metabolic traits. We expect this variation to map to any of ∝300 genes with variants in coding exons or UTRs. One example is a mutation in a key neurotransmitter receptor—Gabra2—that leads to a 3-fold reduction in transcript level in brain. Mapping of behavioral traits in an F2 will result in a large candidate genomic interval of ∝10 cM. This is counterbalanced by the extremely low density of sequence variants in the B6JxB6NJ cross—3.6 and 8.2 variants/Mb for SNPs and indels, respectively. Our approach will facilitate discovery of genes and variants that control behavioral and metabolic phenotypes.

[1] The University of Tennessee Health Science Center, Memphis TN, USA



TUESDAY
MAY 21

poster #35

Identifying neuropeptides induced by exposure to a cocaine-associated context and exercise in male C57BL/6J mice

ML Mustroph [1, 2, 5,] S Dowd [1, 4], EV Romanova [1, 4], JV Sweedler[1, 4], CN Kilby 1 & JS Rhodes [1, 3, 5]

I recently showed that wheel running can facilitate extinction of conditioned place preference (CPP) for cocaine if running occurs after conditioning. However, mechanisms underlying CPP extinction from running are unknown. Given that the hippocampus and amygdala play an important role in contextual conditioning, it is reasonable to hypothesize that neuroadaptations from running in these regions underlie the rapid extinction of CPP. In my current research, I am determining whether the accelerated extinction of cocaine CPP is associated with altered expression of neuropeptides in hippocampus and amygdala of C57BL/6J mice. The proposed research is innovative because it uses a peptidomics approach to identify known and novel neuropeptides that interact with running and cocaine reward. Once these neuropeptides are identified, developing effective treatments to help maintain abstinence from drug addiction may become possible.

[1] Beckman Inst., [2]Col. of Med., [3]Dept. of Psychology, Chemistry Department[4, 5]Neurosci. Program, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Funding Source: NIH grants MH083807 AND DA027084? to JR and Beckman Institute Graduate Fellowship to MM

TUESDAY
MAY 21

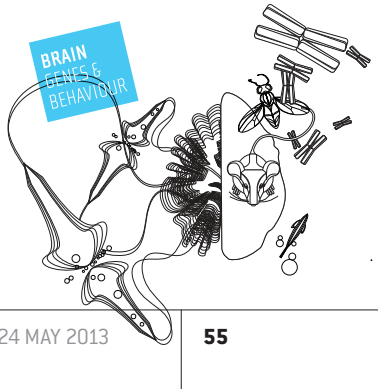
poster # 36

Cross-talk of genetic and environmentally modulated epigenetic factors in the development of anxiety-related behavior: in-depth analyses of candidate genes

Roshan R. Naik[1], Sergey Sotnikov[1], Ludwig Czibere[1], Rainer Landgraf[1]

Most psychiatric disorders display complex phenotypic patterns and are commonly accepted to have a complex genetic basis, where huge sets of alleles determine individual vulnerability to the respective disorders. Among the phenotypic aspects, anxiety-related behavior is an intricate interplay of genetic and environmental factors, where previous research in our group has shown that environmental enrichment (EE) and unpredictable chronic mild stress (UCMS) can bidirectionally modulate the anxiety-related phenotype of bidirectionally bred high (HAB) and low (LAB) anxiety mice, respectively, shifting it from both extremes towards "normal".
Towards this end, we utilized quantitiative PCR to measure mRNA expression of various candidates genes implicated in the extremes of trait anxiety. Several candidate genes were found to be differentially expressed in limbic brain regions. For example, Tmem132d is a novel candidate which has been previously shown to be higher expressed in the anterior cingulate cortex of HABs and also in the frontal cortex of panic disorder and unipolar depressed patients. Genetic characterization of Tmem132d revealed two single-nucleotide polymorphisms (SNPs) in the 1000 bp promoter region. Using in vitro promoter assays, we revealed these SNPs to cause differential expression of Tmem132d mRNA.
Moreover, to study cis-trans interaction that causes differential expression, we cross-mated HAB x LAB to obtain heterozygous F1 offspring carrying both HAB and LAB alleles in the same pool of trans-acting factors. Here, we show how beneficial (EE) vs. detrimental (UCMS) environmental manipulations to the same F1 offspring causes differential changes in allelic expression and corresponding phenotypic changes.

[1] Max Planck Institute of Psychiatry, Munich 80804, Germany.



TUESDAY
MAY 21

poster # 37

The role of striatal acetylcholine in cognition: Behavioural phenotyping of mice deficient for vesicular acetylcholine transporter (VAChT)

Palmer, D. [1,3], Gahnsmith, K. [1], Courtney, R. [1], Plumb, I. [1], Bulosan, B. [1], Binsell, E. [1], Van Maanen, A. [1], Prado, V. F. [2], Prado, M. M. [2], Choleris, E. [1,3], & Winters, B. D. [1,3]

Much of the work investigating the role of acetylcholine in cognition has focused on neurons within the basal forebrain; however, the striatum contains an independent cholinergic system. The role of striatal cholinergic neurons in cognition and behaviour remains unclear. Here we present data from a genetic mouse model that has disrupted cholinergic transmission in the striatum due to localized knockout of the Vesicular Acetylcholine Transporter (VAChT). The goal of the present research is to further characterize striatal cholinergic activity by assessing mice on a cognitive battery. Additionally, the question of whether there are sex differences in striatal cholinergic activity was addressed by testing males and females. Results from social and object recognition paradigms have revealed specific impairment in mice deficient for striatal acetylcholine when tested at 5-minute or 15-minute retention delays. The impairment was more severe in female mice than males.
This impairment was not present in 3-hour delay tasks in either sex. Furthermore, the knockout mice displayed normal performance on an object location paradigm at all delays. Analysis of performance of the mice in the 5-choice serial reaction time test (5-CSRRT) revealed specific impairments in task accuracy and trial omissions. These mice are also currently being tested on visual pairwise discrimination and reversal tasks. These results provide novel insight into the cognitive functions of striatal cholinergic transmission and suggest hitherto unrecognized contributions to short-term recognition memory and attention.

[1] Department of Psychology, University of Guelph, Guelph, ON, Canada
[2] Department of Physiology and Pharmacology, Western University, London, ON, Canada
[3] Collaborative Neuroscience Program, University of Guelph, Guelph, ON, Canada

Funding: NSERC

TUESDAY
MAY 21

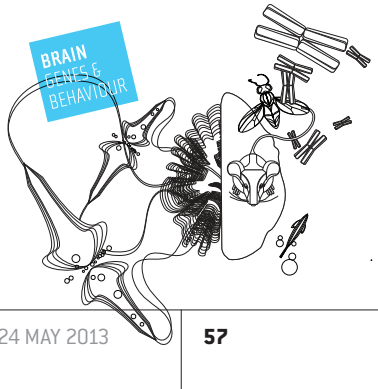
poster #38

The selection for "cognitive" trait in mice. Is it possible?

Olga Perepelkina[1], Vassilissa Golobrodo[1], Irina Lilp[1], Inga Poletaeva[1]

The terms "cognitive behavior" and "cognitive trait" are used in most case in their broadest sense. This id based on serious grounds as learning, attention, exploration are the features which are essential for the cognitive behavior to be performed. At the same time "animal cognition" could be considered as the adaptive behavioral act based on the understanding by animal the logic structure of the task. The animal ability to extrapolate the direction of food bait movement when it disappears from view is the cognitive trait in the latter sense, being the elementary logic task. This ability demonstrated individual variability with the genetic component. The selection of mice for high scores of extrapolation task solution was started in 2009 from genetically heterogeneous population (further maintained simultaneously as the control). The parents for each next generation of the new line EX were chosen on the basis of correct 1st test solution, 5 or 6 successful solutions (out of 6), and they should not display anxiety during trials (elevated locomotion, refusals to approach food etc). More than one hundred mice were tested in each generation. The selection was the success for the decrease of anxiety, while no differences from controls were found in logic task solution success. At the same time EX mice demonstrated significantly higher scores in the puzzle-box cognitive task. Thus it spite of no direct success in this selection, differences in some other behavioral traits appear. The variability of trait scores in different selection generations were found.

[1] Biology Department, Lomonossov Moscow State University, Moscow, Russia, RFBR grant N 10-04-00891, Russia



TUESDAY
MAY 21

poster #39

Automated assessment of motor learning and motor performance using the Erasmus Ladder: a novel tool for the rapid phenotyping of mice

SKE Koekkoek [1], RF Roelofs [2], CP Boele [1], CI De Zeeuw [1]

Recent developments in the creation of mouse models for human diseases have called for tools that are able to quickly screen mutant mice for their motor phenotype. In our department, we have developed two successful tools for detecting mouse mutants with cerebellar deficits: eye blink conditioning and vestibulo-ocular reflex (VOR) adaptation. However, for screening large amounts of mice these systems are too time consuming, as they require specialized and invasive surgery. Therefore we developed a new high throughput tool, the Erasmus Ladder: a fully automated test for detecting motor performance and learning deficits.
The Erasmus Ladder is a horizontal ladder with two cages on its opposite ends. Mice are trained to walk with a constant speed from one cage to the other. All subdivisions of the rungs are equipped with a pressure sensor for detecting footfalls. To facilitate a motor learning paradigm the rungs can be automatically protracted and retracted based on the position and speed of an approaching animal. During conditioning trials, a randomly selected rung rises 12 mm above the walking level to create a perturbation. This unconditioned stimulus occurs at a fixed moment after the onset of the conditioned stimulus (a 15 kHz tone). Both Cx36-/- mutants and lurcher mice reveal difficulties in motor learning (Van Der Giessen et al., 2008).
The advantages of the Erasmus Ladder over eye blink conditioning and VOR adaptation are threefold. First, the experiments do not require surgery; second, the Erasmus Ladder is completely computer controlled; third, the Erasmus Ladder has a feedback control, which allows us to modify the position of rungs during ongoing locomotion.

[1] Department of Neuroscience, Erasmus Medical Center, Rotterdam.
[2] Noldus Information Technology, Wageningen.

TUESDAY
MAY 21

poster #40

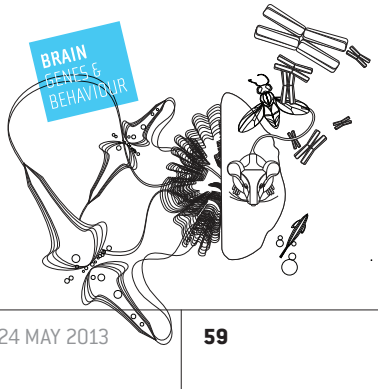
Characterization of neonatal vocal and motor repertoire of Reelin mutant mice

E Romano*[1,3], C Michetti*[2], A Caruso[2], G Laviola[1] and ML Scattoni[2]

Reelin is a large secreted extracellular matrix glycoprotein playing an important role in early neurodevelopment. A reduced Reelin expression has been observed in several brain regions of subjects with autism. Since a number of reports have documented the presence of vocal and neuromotor abnormalities in patients with autism and suggested that these dysfunctions predate the onset of the syndrome, we performed a fine-grain characterization of the neonatal vocal and motor repertoire in reeler mutant mice to explore the developmental precursors of the disorder. Our findings evidence a general delay in motor and vocal development in heterozygous (50% reduced reelin) and reeler (lacking reelin gene) mutant mice. As a whole, an increased number of calls characterized heterozygous pup's emission. Furthermore, the typical ontogenetic peak characterizing wild-type pups on postnatal day 4 appeared slightly delayed in heterozygous pups (to day 6) and was quite absent in reeler littermates. We also detected a preferential use of a specific call category (two-syllable) by heterozygous and reeler mice at postnatal days 6 and 8 as compared to their wild-type littermates. With regard to the analysis of spontaneous movements, a differential profile emerged early in development among the three genotypes. While only slight coordination difficulties are exhibited by heterozygous pups, all items of motor development appears delayed in reeler mice. Overall, our results evidence a genotype-dependent deviation in ultrasonic vocal repertoire and a general delay in motor development in reelin mutant pups.

[1] Behavioural Neuroscience Section, Dept. of Cell Biology & Neuroscience, Istituto Superiore di Sanità, Rome, ITALY
[2] Neurotoxicology and Neuroendocrinology Section, Dept. of Cell Biology & Neuroscience, Istituto Superiore di Sanità, Rome, ITALY
[3] Bambino Gesù Children's Hospital IRCCS, Rome, ITALY
* Equally contributed this work

Supported by the Italian Ministry of Health Grant (GR3), Young Researcher 2008, "Non-invasive tools for early detection of Autism Spectrum Disorders"



TUESDAY
MAY 21

poster #41

An evolutionary approach distinguishes redundant from specific functions for members of the ELAV/Hu pan-neuronal RNA-binding proteins in Drosophila.

X Sun1 and M-L Samson[1]

We are exploring the function of members of the ELAV/Hu family which are conserved RNA binding proteins involved in post-transcriptional regulation. They are early markers of neuronal differentiation first identified in Drosophila melanogaster. Here, we focused on two members of the gene family, fne and rbp9 because of (1) their close relationship to the vertebrate orthologs, (2) the availability of viable null mutants. We are using an evolutionary approach, performing parallel analyses of the fne and rbp9 paralogs, which will add new depth of information about the function of members of this gene family, distinguishing newly evolved functions (specific) from those which are shared and thus more likely to be ancestral.
We will present evidence that fne and rbp9 have both gene-specific functions (relevant to brain anatomy, innate behavior, memory and longevity) and overlapping function(s), as is evident from the lethality in early adulthood of the double mutants. On one hand, we examined the expression of specific genes identified in an RNA-Seq approach as targets of fne (collaboration B. Oliver, NIH, Bethesda, MD, USA) in the context of fne-/ rbp9- single and double mutants. We document a range of situations, from specificity to synergy. The latter reveals functional redundancy and has been observed in the case of the synaptic protein unc-13, a primer of synaptic vesicle exocytosis. On the other hand, male-male interactions in mutants dramatically differ between fne- versus rbp9- mutants, revealing the emergence of a new (or loss of an ancestral) function.

[1] Centre de Neurosciences Paris-Sud UMR 8195, CNRS/Univ. Paris Sud, Orsay F-91405 CEDEX France

Funding Support: CNRS (FRANCE), University of Paris Sud (FRANCE), NIH (USA), Chinese Scholarship Council (CHINA)

TUESDAY
MAY 21

poster #42

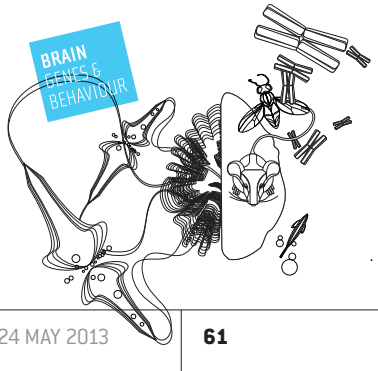
SHANK1 and Autism: Mice Lacking the Post-synaptic Scaffolding Protein SHANK1 Display Communication Deficits and an Aberrant Cognitive Phenotype, but Normal Social Behavior

A.Ö. Sungur1, M.C.E. Jochner[1], R.K.W. Schwarting[1], M. Wöhr[1]

SHANK1 has been identified as a candidate gene for autism spectrum disorders. To test the hypothesis that a mutation in SHANK1 contributes to symptoms of autism, Shank1+/+, Shank1+/-, and Shank1-/- mice were compared in behavioral assays developed to detect deficits in all three autism core symptoms, namely deficits in social behavior, impairments in communication, and repetitive behavior. When assessing isolation-induced ultrasonic vocalizations as a measure for communication during early development, call rate exhibited the typical inverted U-shaped developmental pattern for all genotypes. However, in Shank1-/- pups this pattern was less prominent, with an overall reduced call rate, indicating communication deficits. Social approach behavior was evident irrespective of genotype, with Shank1+/+, Shank1+/- and Shank1-/- showing a preference for the social over the non-social stimulus. Likewise, no genotype differences were observed in the social recognition test. All genotypes preferred the novel over the familiar conspecific. In contrast, object recognition was affected by the Shank1 deletion. Shank1-/- mice showed no preference for the novel object, indicating non-social memory deficits. Shank1+/+ and Shank1+/- mice displayed normal object recognition. Finally, no evidence for increased levels of repetitive behavior in Shank1-/- mice was obtained in the marble-burying test. As compared to Shank1+/+, numbers of marbles buried were reduced in Shank1-/- and Shank1+/- irrespective of social context. Digging and self-grooming behaviors were similar for all genotypes. Together, the present findings indicate that the deletion of Shank1 leads to communication deficits and an aberrant cognitive phenotype, while having relatively minor or no effects on social and repetitive behavior.

[1]Behavioral Neuroscience, Experimental and Physiological Psychology, Philipps-University of Marburg, 35032 Marburg, Germany

Support: Deutsche Forschungsgemeinschaft (DFG – WO 1732/1-1)



TUESDAY
MAY 21

poster #43

A new statistical metric for Drosophila sleep

Sheyum Syed [1]

The fruit fly Drosophila melanogaster has been recently adopted as a model system for the molecular dissection of sleep. With the discovery of several new sleep genes in just over ten years, the fly has already made a significant impact on our knowledge of how sleep is regulated. However, a lack of analytical tools has prevented the detailed interpretation of sleep that is possible in mammals, where sleep is well-established as a multi-stage behavior with a wide variety of physiological correlates. We discuss our initial attempts at moving beyond the current two-stage model of Drosophila sleep and report the establishment of a new metric of fruit fly sleep that can lead to the construction of a sophisticated sleep model in this simple organism. By studying fly sleep-wake transitions at the level of individual events, we show similarities between fruit fly and mammalian sleep architectures. We demonstrate how the distribution of sleep episodes in distinct fly mutants can be quantitatively understood with a simple probability model, similar to a model used to study mammalian sleep. By also examining the temporal organization of sleep, we show that the length of fly sleep events is strongly correlated in time. This gradual increase in mean sleep bout length, we argue, resembles in several ways the mammalian measure of sleep depth. The architectural and temporal similarities reported here between fly and mammalian sleep should further establish Drosophila as a bona fide organism for exploring the fundamental underpinnings of sleep.

[1] Department of Physics, University of Miami, Miami, Florida, USA

Support: XXXX FUNDING

TUESDAY
MAY 21

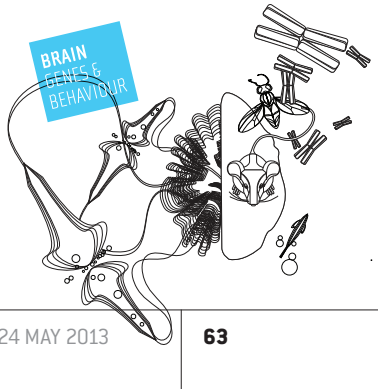
poster #44

Approach-avoidance assays in mice: what are we measuring?

Lisa M. Tarantino[1]

Approach-avoidance assays like the open field, light/dark test and elevated plus maze are widely used animal models of anxiety-like behavior. This group of assays takes advantage of rodents' tendency to avoid brightly lit and/or unprotected areas and their natural curiosity for novel environments. The predictive validity of these assays for anxiolytics has been reported widely in the literature but very few studies have been conducted to examine the effects of various anxiolytics in multiple inbred mouse strains – particularly for behaviors thought to best model anxiety-related behaviors. Furthermore, protocols for measuring behavior in these assays vary from laboratory to laboratory. To validate the use of the open field as an anxiety test in a high-throughput behavioral screen of ENU-mutagenized mice, we tested the ability of a multiple doses of chlordiazepoxide (1, 2, 2.5, 5, 10 and 15 mg/kg), diazepam (1 and 2 mg/kg) and buspirone HCl (0.1, 0.5, 1, 3 and 10 mg/kg) to increase center time. Although CDP increased locomotor activity at most doses, center time was unchanged at lower doses and decreased at higher doses. Doses in this range also failed to increase center time in both BALB/cJ and DBA/2J strains. Two doses of diazepam (1 and 2 mg/kg) also reduced center time in C57BL/6J mice while not affecting locomotor behavior. Buspirone HCl decreased locomotor activity in a dose dependent manner and did not alter center time in C57BL/6J mice. We also assessed behavior in the open field after administration of two doses of the anxiogenic, mCPP (1 and 2 mg/kg). Interestingly, mCPP significantly increased center time in C57BL/6J mice at both doses while increasing locomotor activity at only the higher dose. We will discuss the validity of open field behavior and other commonly-used assays of anxiety in the context of these results.

[1] Department of Psychiatry, University of North Carolina



TUESDAY
MAY 21

poster #45

Asymmetry of the endogenous opioid system in the human anterior cingulate: a molecular basis for lateralization of emotions and pain?

T. Yakovleva [1], S. Fitting [2], H. Watanabe [1], M.Z. Hussain [1], O. Kononenko [1], K. Alkass [3], H. Druid [3], K.F. Hauser [2] and G. Bakalkin [1]

Lateralization of positive and negative emotions and pain suggests an asymmetric distribution of the neurotransmitter systems regulating these functions between the left and right brain hemispheres. The opioid receptor subtypes and their endogenous ligands differentially mediate euphoria or dysphoria, pleasure or pain. We here compared the levels of the opioid receptors and peptides between the left and right anterior cingulate cortex (ACC), a key area for processing of emotions and pain. Opioid mRNAs and peptides along with five "classical" neurotransmitters were analyzed in postmortem tissues from 20 human subjects. Leu-enkephalin-Arg and Met-enkephalin-Arg-Phe, preferential delta/mu- and kappa/mu-opioid agonists demonstrated marked lateralization to the left and right ACC, respectively. No substantial lateralization of mRNAs and neurotransmitters was evident. Analysis of correlations suggested different mechanisms of conversion of kappa-agonist dynorphin B to Leu-enkephalin-Arg in two hemispheres; in the right ACC dynorphin B cleavage may involve PACE4, a proprotein convertase regulating left-right asymmetry formation. Preferential activation of delta/mu- and kappa-receptors known to mediate euphoria and dysphoria, respectively, in the left and right ACC, along with the asymmetry of conversion of kappa- to delta/mu-opioid ligand may be a part of molecular mechanism underlying lateralization of higher functions including positive and negative emotions and pain in the human brain.

[1] Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
[2] Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, Virginia, USA
[3] Forensic medicine, Department of Oncology and Pathology, Karolinska Institute, Sweden

Funding Support: Swedish VR, FAS and FORMAS

TUESDAY
MAY 21

poster #46

High throughput phenotyping of spontaneous behavior: variation within and across 11 inbred mouse strains

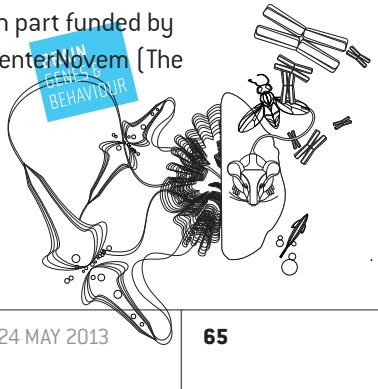
Maarten Loos[1,2]‡, Bastijn Koopmans[1]‡, Emmeke Aarts[3], Gregoire Maroteaux[3], Sophie van der Sluis[3,4], Neuro-BSIK Mouse Phenomics consortium[5], Matthijs Verhage[3,4]‡, August B. Smit[2]‡

Functional genetic analyses, gene finding and pharmacological studies in mice require in-depth knowledge of the behavioral spectrum of the background strains used. We systematically analyzed and compared spontaneous behavior of a panel of commonly used inbred strains (129S1/SvImJ, A/J, C3H/HeJ, C57BL/6J, BALB/cJ, DBA/2J, NOD/LtJ, FVB/NJ, WSB/EiJ, PWK/PhJ and CAST/EiJ) by high-throughput automated home cage observation. Continuous video-tracking observations were segmented into distinguishable behavioral elements, and studied at different time scales, yielding a multivariate set of 115 behavioral parameters of which 105 showed highly significant strain differences. Especially BALB/c, FVB/NJ and C3H/HeJ mice provided extreme values (on 17, 15 and 13 % of the parameters, respectively), whereas C57BL/6J mice showed extreme values on only few parameters (4 %), including habituation, anticipation of the dark phase and maximum velocity. C57BL/6J and BALB/c mice ranked lowest in terms of within-strain variation, especially in comparison to the highly variable 129S1/Sv and DBA/2J strains.
Thus, the C57BL/6J strain is optimal for genetic intervention and pharmacological studies because it shows (i) few extreme values, hence, facilitates detection of both upward and downward phenotypic changes and (ii) low within-strain variation, increasing the statistical power to detect intervention effects. In conclusion, this study shows that genetic background strongly influences spontaneous home cage behavior, and it provides a reference dataset for genetic and pharmacological studies of mouse behavior in the home cage.

[1] Sylics (Synaptologics BV), Amsterdam, The Netherlands
[2] Department of Molecular and Cellular Neurobiology
[3] Department of Functional Genomics, Center for Neurogenomics and Cognitive Research (CNCR), Neuroscience Campus Amsterdam, VU University Amsterdam
[4] Department of Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands &
[5] Collaborators: Brussaard AB, Borst JGG, Elgersma Y, Galjart N, van der Horst GT, Levelt CN, Pennartz CM, Smit AB, Spruijt BM, Verhage M, de Zeeuw CI
‡These authors contributed equally to this work.

Corresponding author
Maarten Loos, Ph.D. Sylics (Synaptologics BV), PO box 71033, 1008 BA, Amsterdam, The Netherlands. E-mail: maarten.loos@sylics.com; Tel: +31 20 5989410; Fax: +31 20 5989281

Support:
S. van der Sluis was financially supported by NWO/MaGW VENI-451-08-025. This study was in part funded by the Dutch Neuro-Bsik Mouse Phenomics consortium, supported by grant BSIK 03053 from SenterNovem (The Netherlands)



WEDNESDAY
MAY 22

PRESIDENTAL LECTURE

Bending the not so simple mind of the fly

Scot Waddell

Directed behaviour emerges from neural integration of sensory stimuli, memory of prior experience and internal states.
We seek an understanding of these conserved neural mechanisms using genetically-encoded tools and the relatively small brain of Drosophila. By temporally controlling neural function memories can be implanted and internal states altered so that most flies behave according to our direction. Such recent studies have revealed a role for distinct subsets of dopaminergic neurons that innervate the mushroom bodies in reward learning and the control of motivated fly behaviour. Therefore, the positive reinforcement system of flies is more similar to that of mammals than previously envisaged.
One might interpret the relative ease of altering behaviour to indicate that everything is simple in the fly brain. However, complexity arises in unexpected ways. Cell-type specific gene expression profiling revealed transposable element expression in long-term memory relevant neurons of the mushroom body. Importantly, brain-specific transposon mobilization is prevalent and likely to be heterogeneous within and between fly brains. Since neural expression and retrotransposition of LINE-1 transposable elements has been observed in mammals, it appears that genomic heterogeneity is a conserved feature of the brain. We propose that it may prove beneficial to specific cell-types and neural processes and could plausibly contribute to behavioural individuality.

[1] Centre for Neural Circuits and Behaviour, Department of Anatomy, Physiology and Genetics, University of Oxford

WEDNESDAY
MAY 22

SYMPOSIUM II

USING ZEBRAFISH TO EXPLORE HOW GENES ... GENERATE BEHAVIOR

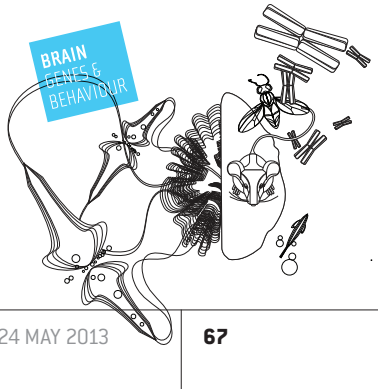
CHAIR: CAROLINE BRENNAN

EMRE YAKSI
Studying neural circuits in genetically tractable model organism

HERWIG BAIER
Optogenetic analysis of zebrafish prey capture behavior

CAROLINE H. BRENNAN
Forward genetic screening for complex behavioural phenotypes

RUI F OLIVEIRA
Rapid regulation of gene expression in the zebrafish brain induced by perceived social interactions



Studying neural circuits in genetically tractable model organism

Emre Yaksi[1]

Understanding how the sensory world is represented in the brain and how these representations generate behaviors that are essential to the life of an organism is the fundamental challenge of sensory neuroscience. The activity of single neurons and the function of synapses have been investigated in great detail. Yet, information processing at the level of the neural circuits is less well understood.
The main goal of our lab is to understand the fundamental principles underlying the function and development of neural circuits in genetically tractable model organisms. We exploit chemosensory systems to achieve this goal. In order to monitor, dissect and perturb the neural circuits of the adult and larval zebrafish brain, we use: two-photon and widefield microscopy, optogenetics, electrophysiological recordings, molecular genetics and behavioral assays. Ultimately, these experiments will help us to understand the fundamental principles of sensory information processing in the brains of vertebrates, including humans. In this talk I will cover a range of technologies for studying zebrafish brain activity and talk about our preliminary findings on sensory computations in zebrafish brain.

[1] NERF, a joint research initiative between imec, VIB and K.U. Leuven Neurophysiology Department - KU Leuven

Optogenetic analysis of zebrafish prey capture behavior

Julie Semmelhack[1], Joseph Donovan[1], Incinur Temizer[1] & Herwig Baier[1]

Neurons form intricate networks through which signals pass at high speed and in complex, dynamically changing patterns. The ultimate task of this nervous activity is the generation of behavior. The goal of our research is to understand how the neuronal pathways in the brain convert sensory inputs into behavioral responses. We use the zebrafish visual system as our experimental model. A moving dot that is displayed on a miniature computer screen is able to elicit a prey capture response in a zebrafish larva. The animal swims toward the wiggling dot on the screen in front of it, in an apparent attempt to catch this “virtual prey”. With the help of two-photon GCaMP5 imaging, we are observing how neurons in the fish brain process these visual stimuli and generate motor commands. Targeted activation of optogenetic effectors, such as Channelrhodopsin (ChR2) and Halorhodopsin (eNpHR), allows for the remote optical control of brain function. With this method, and a battery of others, we are now identifying the circuit components whose activity is necessary and sufficient to evoke and control prey capture behavior.

[1] Max Planck Institute of Neurobiology, Department Genes – Circuits – Behavior, Am Klopferspitz 18, 82152 Martinsried, Germany

Forward genetic screening for complex behavioural phenotypes

Matthew O. Parker[1], Alistair J. Brock[1], Mollie E. Millington[1], Fraser J. Combe[1] and Caroline H. Brennan[1]

Zebrafish are an established vertebrate, genetic model system, well placed to give insights into genetic factors and cellular processes controlling behaviour: as a result of the zebrafish mutagenesis project being undertaken by the Sanger Institute, there are a large number of zebrafish lines that carry mutations in known and unknown genes that can be screened for alterations in behavioural phenotypes. We have developed and automated assays of core component behaviours associated with psychological disease and addiction and used these to screen lines of mutagenized zebrafish. Using a conditioned place preference approach we have identified alleles associated with increased drug seeking behaviour. We have used a zebrafish version of the 5 choice serial reaction time task to identify lines with subtle differences in learning behavior, attention and impulsivity profiles. We provide evidence for a role of cholinergic signaling via nicotinic receptors in zebrafish impulse control.

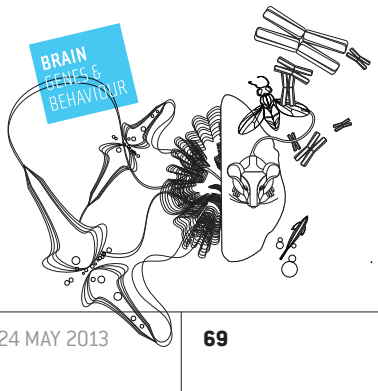
[1] School of Biological and Chemical Sciences, Queen Mary University of London, London E1 4NS

Rapid regulation of gene expression in the zebrafish brain induced by perceived social interactions

Rui F Oliveira[1]

Social interactions have profound effects on the physiology and behavior of animals. Socially driven behavioral changes are an adaptation that allows animals to adjust their behavior according to the nuances of daily social life and to transitions between life-history stages. This social plasticity depends on neural plasticity and neuromodulation of the circuits underlying social behavior. Here I present data on social regulation of gene expression in the zebrafish brain using microarrays. Short-term (30 min) behavioral interactions have a significant impact on the brain transcriptome, with winners and losers being differentially affected whereas individuals that fight their own image on a mirror and thus express aggressive behavior but do not perceive a change in social status (neither win nor lose the fight) show no significant changes in brain transcriptome. Differentially expressed genes include immediate early genes (c-fors, egr-2) and effector genes involved in social plasticity (e.g. bdnf, npas4). Gene ontology and pathway analysis reveals that differentially expressed genes form functional groups and that the MAP kinase pathway is significantly enriched. Together these results indicate that social interactions common in the daily lives of animals have a significant impact on their brain transcriptome, and that it is the perceived situation and not the objective structure of the social interaction that triggers the response. Given that some of the differentially expressed genes are involved in the molecular pathways of memory consolidation it is possible that the memory of ambiguous social interactions (i.e. without a clear outcome) is not being consolidated in long-term memor

[1] ISPA- Instituto Universitário & Champalimaud Neuroscience Program at Instituto Gulbenkian de Ciência, Lisboa, Portugal



WEDNESDAY
MAY 22

SYMPOSIUM III

NOVEL MECHANISMS IN ANXIETY AND DEPRESSION
CHAIR: STEPHANIE DULAWA

STEPHANIE DULAWA
Serotonin 2C antagonists as putative fast-onset antidepressants.

ABRAHAM PALMER
Mechanistic studies of Glo1 and behavior

IIRIS HOVATTA
A cross-species approach to identify anxiety-associated transcript networks

JOHN F. CRYAN
GABA-B receptor subunit isoforms differentially mediate susceptibility to early-life stress-induced depression related behaviour

Serotonin 2C antagonists as putative fast-onset antidepressants

Stephanie Dulawa[1]

Current antidepressants must be administered for several weeks to produce therapeutic effects. This therapeutic delay increases the burden of illness and suicide risk. Novel antidepressants with a faster onset and novel therapeutic mechanisms are greatly needed. Using mouse models of chronic antidepressant action, we found that selective serotonin 2C (5-HT2C) antagonists display antidepressant effects with a faster-onset (5 days) than that of classical antidepressants. Five days of treatment with 5-HT2C antagonists reduced immobility in the forced swim test, reversed chronic mild stress (CMS)-induced reductions in sucrose preference, and reversed hyperlocomotion induced by olfactory bulbectomy. This regimen with 5-HT2C antagonists also increased levels of phosphorylated CREB and BDNF protein in the prefrontal cortex (PFC), which are classical markers of antidepressant action. Five days of treatment with the 5-HT2C antagonist SB 242084 also reversed CMS-induced dendritic atrophy, and increased the apical spine density of layer II/III pyramidal neurons in medial PFC. None of these effects were observed following five days of treatment with citalopram, a prototypical serotonin selective reuptake inhibitor.
Our findings identify 5-HT2C antagonists as putative fast-onset antidepressants, and implicate induction of BDNF and synaptic spines in medial PFC pyramidal neurons in rapid antidepressant onset.

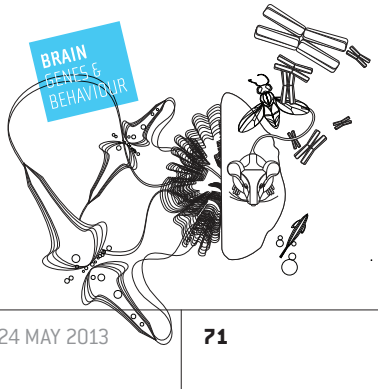
[1] Department of Psychiatry and Behavioral Neuroscience, The University of Chicago, Chicago, IL 60637, USA

Mechanistic studies of Glo1 and behavior

Abraham Palmer[1]

Numerous mouse genetic studies have identified associations between the expression of Glyoxalase 1 (Glo1) and anxiety-like behavior; however, the underlying mechanism has been elusive. We have previously shown that a common genomic duplication that is present in about 1/3 of inbred mice leads to the duplication or triplication of Glo1, which is responsible for previously observed expression differences among inbred and outrbred mice. Glo1 is an enzyme that detoxifies methylglyoxal (MG). We have recently established that Glo1 expression increases anxiety by reducing MG levels. Mice with a transgenic bacterial artificial chromosome containing Glo1 displayed increased anxiety-like behavior and reduced MG concentrations. Acute administration of MG reduced anxiety-like behavior and, at higher doses, caused locomotor depression, ataxia, and hypothermia; effects that are characteristic of GABA-A receptor activation. When applied to primary cerebellar granular neurons in culture, physiological concentrations of MG selectively activated GABA-A receptors with about 1/3 the potency of GABA. These effects could be blocked by the GABA-A selective antagonist SR-95531. Competition studies suggest that GABA and MG may compete for the same binding site. Taken together our data establish that Glo1 expression increases anxiety by reducing levels of MG, thereby altering GABA-A receptor activation. More broadly, they provide a link between metabolic state, neuronal inhibitory tone, and behavior. Finally, they point the way toward potentially novel pharmacological interventions.

[1] Department of Human Genetics, The University of Chicago, Chicago, IL 60637, USA



A cross-species approach to identify anxiety-associated transcript networks

Iiris Hovatta[1]

Anxiety is an evolutionarily conserved response to a threatening situation and the genetic basis of anxiety is expected to be partially conserved between mice and humans. We are using functional genomics approaches to identify transcript networks, comprising of mRNAs and miRNAs, that regulate anxiety-like behavior in mice. As a model we use six inbred mouse strains that differ between their innate anxiety-like behavior. We have carried out miRNA-seq and mRNA-seq in frontal cortex, hippocampus, and hypothalamus and identified a number of miRNAs that correlate with anxiety-like behavior in this model. We predicted target mRNAs for these miRNAs. Since genuine miRNA-target mRNA pairs are expected to be anti-correlated we selected such pairs for pathway analysis. One pathway involving several functionally connected genes included NFKB transcription factor as a hub gene. We subsequently carried out a genetic association analysis in a human anxiety disorder cohort to show that variants in the NFKB1 gene show evidence for association to anxiety disorders. These results support the notion that cross-species approaches are valuable in identification of genes that regulate anxiety in mice and humans. Through identification of such genes we will better understand the molecular basis of anxiety, a prerequisite for development of targeted therapies.

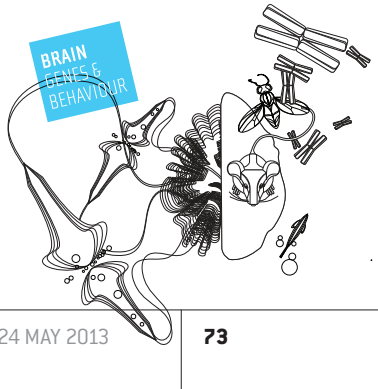
[1] Department of Biosciences, University of Helsinki, 00790 Helsinki, Finland

GABA-B receptor subunit isoforms differentially mediate susceptibility to early-life stress-induced depression related behaviour

John F. Cryan[1]

Interactions between genetic risk factors and adverse environmental conditions during early-life are important susceptibility factors for the development of depression and anxiety disorders. GABA-B receptors have been implicated in the pathophysiology of depression and anxiety disorders. The GABA-B receptor is an heterodimer composed of a GABA-B(1) and GABA-B(2) subunit, with the GABA-B(1) receptor subunit existing as two isoforms, GABA-B(1a) and GABA-B(1b). The generation of mice lacking either isoform permits the elucidation of the role for these isoforms in physiology and behavior. It is unclear whether either isoform plays a role in determining susceptibility or resilience to the development of depression- and anxiety-like behaviors in adulthood following early-life stress. Thus, GABA-B(1a)-/- and GABA-B(1b)-/- mice were maternally separated (MS) for 3 hours from postnatal day 1 to 14, or remained undisturbed in their home cage (non-separated, NS). Ultrasonic vocalizations (USVs) of the pups were measured during separation from the dam on PND1 and PND7 to assess anxiety. During adulthood, anxiety- and depression-like behaviors were assessed in MS and NS mice. Results revealed a gene x environment interaction with GABA-B(1a) and GABA-B(1b) isoforms differentially modulating susceptibility to depression-like behavior in adulthood following early-life stress. Specifically, mice lacking the GABA-B(1b) isoform were resilient to early-life stress-induced anhedonia, and exhibited an antidepressant-like phenotype under baseline conditions. These results highlight the importance of gene x environment interactions during early-life as a risk factor for the development of psychiatric disorders in adulthood. Moreover, GABA-B1 receptor subunit isoforms represent novel targets for the development of new antidepressant therapies.

[1] Departement of Anatomy & Neuroscience, University College Cork, Ireland



WEDNESDAY
MAY 22

SYMPOSIUM IV

HIPPOCAMPUS AND COGNITIVE SPATIAL MAPS: MULTI-SPECIES COMPARISON

CHAIR: HANS PETER LIPP
CHRISTOPHER JANUS

CHRISTOPHER JANUS
Of Mice and Man: murinizing human behavior

H.-P. LIPP
Non-spatial functions of the hippocampus: adaptation of hippocampally lesioned mice to naturalistic environments

LARS LEWEJOHAN
Spatial learning of wild and domestic guinea pigs

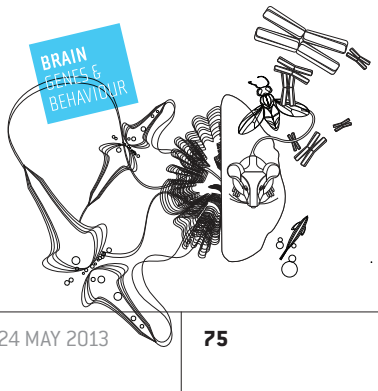
M LIEDVOGEL
The genetics of migration

Of Mice and Man: murinizing human behavior

Christopher Janus [1], Emily Baker[1], Callie Dunn[2], Russell Bauer[2]

Many neurological disorders manifest numerous behavioural abnormalities accompanied by slowly progressing cognitive decline. The long prodromal period of these disorders often impedes effective preventive interventions preceding clinical diagnosis. In the field of Alzheimer's disease (AD), deficits in short-term memory and spatial orientation occur in patients at the earliest stage of cognitive impairment. This hippocampus dependent decline in spatial navigation has been reliably replicated in mouse models of AD as impairment in the reference memory version of the water maze. Our previous work
has shown that mice modeling AD were incapable of efficiently utilizing spatial strategies in this task, but they were capable of solving the task using alternative strategies. We have recently used computerized version of virtual water maze test to evaluate spatial navigation and reference memory in young and old normal humans. We demonstrated a decline in spatial navigation ability in normally aged subjects that worsened with transition to mildly cognitively demented patients. Here, we present the analysis of the spectrum of search strategies employed by young and aged subjects during navigation in the virtual environment, and attempt to derive commonalities with strategies used by mice in the real task. These parallel, parametrically matched mouse-human comparative studies, which address the same memory system and behavioural modality, should help to validate the mouse-human translational models. The comparative approach should also help to
identify accurate behavioural biomarkers, which would be sensitive in early pre-clinical identification of individuals at-risk of developing AD.

[1] Center for Translational Research in Neurodegenerative Disease (CTRND), and Department of Neuroscience, University of Florida
[2] Department of Clinical & Health Psychology, and Department of Neurology, University of Florida



Non-spatial functions of the hippocampus: adaptation of hippocampally lesioned mice to naturalistic environments

H.-P. Lipp[1], Alexei L. Vyssotski[1], Rob Deacon[2], Mike Galsworthy[1], Inga I. Poletaeva[3], Nada Ben Abdallah[1], Giacomo Dell'Omo[1], David P. Wolfer[1]

Traditionally, the hippocampus is thought to be a substrate for spatial reference memory in rodents. To validate this assumption, we have tested mice with complete bilateral hippocampal lesions and sham lesioned mice first in the laboratory and then in naturalistic outdoor pens in western Russia. In the laboratory, the mice showed severe deficits in water maze learning, including finding a cued platform, and were deficient in adaptation to visit food stations in IntelliCage. In the field, the mice were tested for deficits in hippocampus-dependent naturalistic tasks such as food burrowing and foraging in foodsupplemented feeders. After adaptation to feeders, the lesioned and control mice were released into outdoor enclosures, equipped with automated feeders delivering food to a transponder-tagged mouse. Mice lived in a protected shelter and could freely patrol the feeders. Despite of the successful adaptation, half of the lesioned mice did not survive the first two days. The remaining lesioned animals survived well for two weeks, as did all controls, and visited the feeders regularly. However, in comparison to sham controls, they were hyperactive and committed many entry errors, and lost recognizable circadian activity patterns. These data indicate that the hippocampus of mice is deeply involved in regulation of species-specific behavior required to adapt to new situations, and that the typical spatial learning tasks in the laboratory catch only a fraction of probably less important deficits due to hippocampal malfunction.
Thus, translational studies should always include testing of ethologically relevant tests in order to validate putative memory problems.

[1] Institute of Anatomy, University of Zurich, Switzerland
[2] Dept., of Psychology, University of Oxford, UK
[3] Laboratory of Physiology and Genetics of Behavior, Faculty of Biology, Moscow State

Spatial learning of wild and domestic guinea pigs

Lars Lewejohan[1]

The process of domestication of the domestic guinea pig starting at least 4500 years ago, led to changes in anatomy, physiology, and behavior compared with their wild relative, the wild cavy. One striking domestic trait is a reduction in relative brain size, which in the domesticated form of the guinea pig amounts to 13%. Although domestic guinea pigs are widely used as a laboratory animal, learning and memory capabilities are often disregarded as being very scarce. Even less is known about learning and memory of wild cavies.
Here we compared the spatial learning abilities of wild and domestic guinea pigs of both sexes using the Morris water maze. Both, wild cavies and domestic guinea pigs were able to learn the task, proving the water maze to be a suitable test for domestic and wild guinea pigs. Regarding the speed of learning, male as well as female domestic guinea pigs outperformed their wild conspecifics significantly. Interestingly, only domestic guinea pigs showed a significant spatial association of the platform position, while wild cavies used other effective search strategies. The results demonstrate that despite reduced relative brain size domestic guinea pigs do not at all perform worse than their wild relatives in tests of spatial learning abilities. Hence, artificial selection and breeding did not lead to a cognitive decline but rather to an adaptation to man-made environment that allows solving the task more efficiently.

[1] Dept. of Behavioural Biology, University of Muenster, Germany

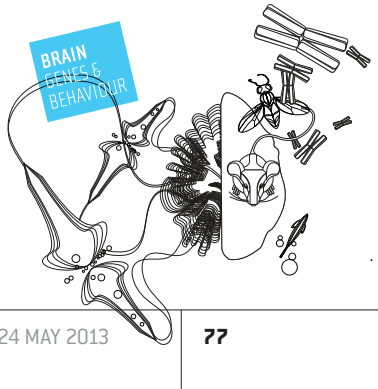
The genetics of migration

M Liedvogel[1]

Migratory birds possess an inherent time schedule and at least an inherited initial migratory direction to cope with the challenge of migration. But what are the number and identify of genes controlling this phenotype? With the work presented here we are currently evolving the field of bird migration from phenotypic to molecular approaches.

Our knowledge about the genetics of migration today is still mainly based on crossbreeding and displacement experiments, and even though a heritable basis of migratory traits is well accepted, virtually nothing is known about the genes shaping these traits. Our research focuses on two subspecies of the willow warbler Phylloscopus trochilus in Northern Europe. The subspecies are morphologically and genetically extremely similar, but they have clearly differing migratory orientation programmes and winter in dissimilar areas in Africa. To detect genes potentially involved in migratory traits, we use traditional population genetics and next-generation sequencing approaches to identify genes encoding for intraspecific
variation of the migratory programme.

[1] Lund University, Department Biology, Sölvegatan 37, Sweden



THURSDAY
MAY 23

KEYNOTE LECTURE

Neural mechanisms of social risk for psychiatric disorders

Andreas Meyer-Lindenberg[1]

Multiple genetic and environmental risk factors for the multifactorial brain disorder, schizophrenia, have been identified through epidemiological and genetic research in the preceding decades.
A major translational research strategy is to try and elucidate how these confirmed risk factors act on brain to increase risk for the disorder.
In this talk, we will review this strategy, using both genetic and environmental risk factors as examples. In genetic risk, we will focus on genome-wide identified single nucleotide polymorphisms in or near the genes ZNF804A and CACNA1C. In environmental risk, we discuss recent work relating urbanicity and migration status to risk for schizophrenia. Our data show that neural effects of epidemiologically validated risk factors can be elucidated in human brain that mirror intermediate phenotypes found in subjects with the illness and their relatives. Specifically, connectivity of lateral prefrontal cortex with striatum, midbrain and hippocampus can be shown to be impacted by genetic risk, and a medial prefrontal circuit regulating amygdala and be extended limbic system, previously implicated in the processing of negative emotion, can be linked to environmental risk factors. Taken together, this research begins to define a neurogenetic and neuroenvironmental risk architecture for schizophrenia that improves our understanding of the pathophysiology of the illness and may point the way to new treatment targets.

[1] Central Institute of Mental Health, Department of Psychiatry and Psychotherapy, University of Heidelberg/ Medical Faculty Mannheim, Germany

THURSDAY
MAY 23

SYMPOSIUM V

GENETIC REGULATION OF ETHANOL SENSITIZATION IN FLIES, MICE, AND HUMANS

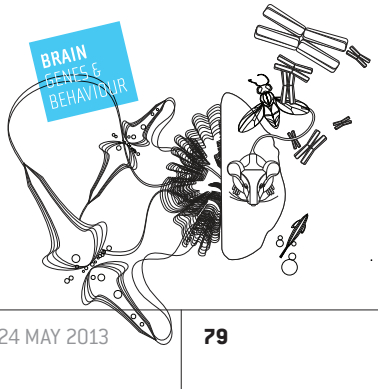
CHAIR: STEPHEN BOEHM
TAMARA PHILLIPS

GALIT OPHIR
Sexual deprivation increases ethanol intake and modulated social avoidance behavior in Drosophila

D. N. LINSENBARDT
Determining the heritability of locomotor sensitization to ethanol and its relationship to ethanol's positive motivational effects in mice

MICKAEL NAASSILA
Brain chromatin remodeling a novel potential pharmacological target in ethanol-induced sensitization

ANDREA KING
Alcohol Response Phenotypes and Future Excessive Drinking in Humans



Sexual deprivation increases ethanol intake and modulated social avoidance behavior in Drosophila

Galit Ophir1 and Ulrike Heberlein[1]

Natural rewards and abused drugs affect the function of the brain's reward systems, and abnormal function of these brain regions is associated with addictive behavior. Some aspects of drug reward can be modeled in the genetically tractable fruit fly Drosophila melanogaster. Flies exhibit complex addiction-like behaviors, including a lasting attraction for a cue that predicts ethanol intoxication and a preference for consuming ethanol-containing food, even if made unpalatable. In addition to genetic factors, social experience can affect drug addiction. We therefore investigated the relationship between sexual experience and alcohol preference in Drosophila. In males, mating increased Neuropeptide F (NPF) levels, whereas sexual deprivation reduced NPF. Moreover, activation or inhibition of the NPF system reduced or enhanced ethanol preference, respectively. These results thus link sexual experience, NPF system activity, and ethanol consumption. In addition, artificial activation of NPF neurons was in itself rewarding and precluded the ability of ethanol to act as a reward. We propose that activity of the NPF/NPF receptor axis represents the state of the fly reward system and modifies behavior accordingly. The modulation of NPF system by socially rewarding and non-rewarding experiences reflects a broader mechanism by which experience is represented in the brain and converted into changes of circuit function and eventually modulation of behavior. To extend our understanding of this process we are analyzing the transcriptional profile of social experience within specific subsets of neuromodulatory circuits and relating it to changes in fly's social group dynamics as an output behavior.

[1] HHMI Janelia Farm Research Campus

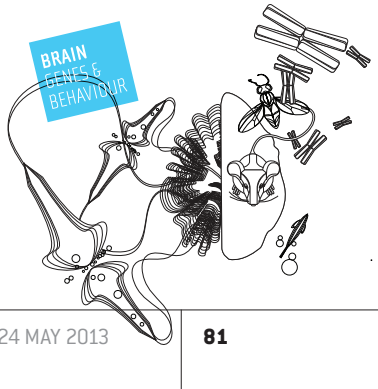
Determining the heritability of locomotor sensitization to ethanol and its relationship to ethanol's positive motivational effects in mice

D. N. Linsenbardt[1] & S. L. Boehm II[1]

Sensitization to the locomotor stimulant effects of alcohol (ethanol) is thought to be a heritable risk factor for the development of alcoholism that reflects progressive increases in the positive motivational effects of this substance. However, very little is known about the genetic influences involved in this phenomenon or the extent to which ethanol's positive motivational effects are altered in parallel to its development. The first goal of this work was to determine the heritability of ethanol-induced locomotor sensitization using short-term behavioral selection. C57BL/6J (B6) x DBA/2J (D2) F2 mice were phenotyped for the expression of locomotor sensitization, and bred for high (HLS) and low (LLS) expression of this behavior. A secondary goal was to characterize possible line differences in ethanol's positive motivational effects using conditioned place preference (CPP) and a limited access voluntary ethanol consumption assay known as Drinking-in-the-Dark (DID). Genetic differences accounted for 22% (h2=.22) of the observed line differences in locomotor sensitization. However, whereas there were no significant differences in CPP between lines, there were marginal differences (p=.06) in ethanol consumption (albeit in females only) with LLS mice generally consuming more ethanol than HLS mice. That changes in ethanol sensitivity following repeated exposures are in part genetically regulated highlights the relevance of studies aimed at determining how genes regulate susceptibility to ethanol-induced behavioral and neural adaptations. Additionally, line differences in ethanol intake but not ethanol-induced CPP suggest that the utility of locomotor sensitization as a model of alterations in ethanol's positive motivational effects in mice is still unclear.

[1] Psychobiology of Addictions, Department of Psychology and Indiana Alcohol Research Center, Indiana University – Purdue University Indianapolis, Indianapolis, IN 46202

Acknowledgments: This work was funded by NIAAA grant #s AA015434 (SLB), AA016789 (SLB), and AA07462 (DNL)



Brain chromatin remodeling a novel potential pharmacological target in ethanol-induced sensitization

Béatrice Botia[1], Mickael Naassila[1], Rémi Legastelois[1]

Ethanol - induced behavioral sensitization (EIBS) is thought to be a model of neuroplasticity since the enduring changes in behavior may be associated with long term changes in brain gene expression even after protracted 'abstinence'. Recent data suggested that long term changes in gene expression may be mediated by epigenetic regulations (such as histone acetylation) and that ethanol can alter the activity of enzymes involved in chromatin remodeling. In the present work, we screened differential gene regulations (gene families involved in Ca2+ signaling and epigenetics) occurring between mice prone and resistant to EIBS. We also investigated the effect of the pharmacological blockade of histone deacetylases (HDAC) on both the induction and expression of EIBS and looked for potential gene regulations mediating the effect of HDAC inhibitor. Finally we were interested in exploring whether anxiety plays a role in EIBS as well as whether a correlation between the propensity to drink ethanol and EIBS vulnerability does exist. Our results showed that that the contrasted behavioral response to an ethanol challenge between resistant and sensitized mice may be mediated by epigenetic mechanisms occurring specifically in the striatum. The HDAC inhibitor blocked EIBS induction or expression depending on the ethanol dose. Among the gene regulations that may explain the effect of HDAC inhibitor on EIBS we identified BDNF as a putative candidate. Finally, our correlation studies of anxiety and propensity to drink ethanol with EIBS showed promising results on these two traits on the vulnerability to develop EIBS.

[1] Research Group on Alcohol & Pharmacodependences (GRAP) – INSERM Unit ERi 24, University of Picardie Jules Verne, FRANCE

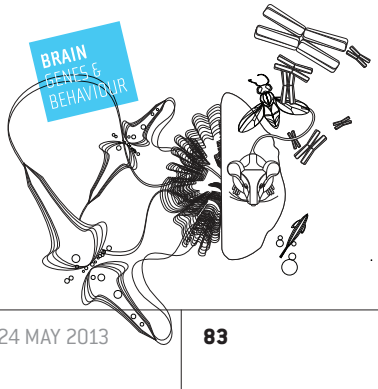
FUNDINGS: ANR grant SENSIBALCO

Alcohol Response Phenotypes and Future Excessive Drinking in Humans

Andrea King[1]

It is unclear why some individuals escalate their consumption of alcohol over time while others do not. One potential predictor of vulnerability to alcohol use problems is the quality and magnitude of one's acute response to alcohol. This study examined the role of alcohol response phenotype to future drinking in a within-subject, double-blind, placebo-controlled, multi-dose laboratory alcohol challenge study with follow-up of drinking patterns for six years. Participants were non alcoholic heavy drinkers (n=104) and light drinker (n=86) controls. Laboratory sessions (570 total) examined each participants' subjective responses to a high (0.8 g/kg) and a low dose of alcohol (0.4 g/kg) and a placebo. Follow-ups were conducted quarterly for the first two years and extended annually through six years with an overall 98% follow-up rate. Alcohol produced greater stimulant and rewarding (liking and wanting) responses and lower sedative and cortisol responses in heavy versus light drinkers. In heavy drinkers, those with heightened stimulating and rewarding responses to alcohol and lower sedative responses engaged in more frequent future binge drinking through follow-up and experienced more drinking consequences. In light drinkers, no alcohol response factors predicted drinking, which was largely low-risk throughout follow-up. The findings offer new empirical insights into the propensity for excessive alcohol drinking: heightened sensitivity to rewarding effects of alcohol is a robust predictor of future habitual binge drinking behaviors during a developmental interval when many participants were entering their third decade of life, when binge drinking behaviors are less normative and continued alcohol misuse becomes more severe.

[1] University of Chicago



SELECTED TALKS SESSION I

High-Resolution Mapping of Multiple Neuronal Traits in an Outbred Population of Mice by Reconstruction of Complete Genomes Using Ultra-Sparse (0.1X Coverage) Sequencing

Jérôme Nicod[1], Leo Goodstadt[1], Cai Na1, Carl Hassett[2], Xiangchao Gan[1], Russell Joynson[2], Hayley Page[2], Clare Rowe[2], Barbara Nell[2], James Cleak[1], Polinka Hernandez-Pliego[1], Paul Potter2, Richard Mott[1], Tom Weaver[2], Jonathan Flint[1]

Advances in next generation sequencing have brought closer the possibility of performing genome wide association studies (GWAS) on fully sequenced individuals. Currently, however, costs are still prohibitive. Here we show that it is possible to reconstruct the complete genomes of thousands of individuals using ultra-sparse sequencing, thus making sequencing a practical alternative to genotyping. When a population is known to descend from a relatively small set of founders the haplotypes of the descendants can theoretically be reconstructed even when only little genetic information is available. We have previously demonstrated that commercially available outbred mice may be suitable for GWAS [Yalcin et al, PLoS Genet, 2010]. With relatively low linkage disequilibrium (LD) and a lack of rare alleles, these populations offer the possibility to map complex traits at high resolution. In the present study 2000 mice from one such commercially available outbred population were tested for multiple behaviour traits. These include anxiety (elevated plus maze and open field), depression (Porsolt swim test), pre-pulse inhibition of startle, sleep, fear conditioning and male courtship vocalization. Finally all animals had their genomes sequenced at low (0.1x) coverage. The sparse raw sequencing data was checked for similarity with complete sequences of 13 laboratory inbred strains and, by imputation using a Hidden Markov Model, the whole genomes were reconstructed from the ancestor haplotypes. We have used the ancestor haplotypes dosage at each locus for the traits mapping and we will present the first QTLs identified. This new approach to reconstruct complete genome sequences opens up the possibility of testing all genetic variants across the genome for identifying loci associated with phenotypes of biological interest despite ultra-low coverage sequencing.

[1] Wellcome Trust Centre for Human Genetics, Oxford, UK
[2] Mary Lyon Centre, MRC Harwell, Harwell Science and Innovation Campus, UK

SELECTED TALKS SESSION I

DNA methylation analysis of the human brain: Alzheimer disease

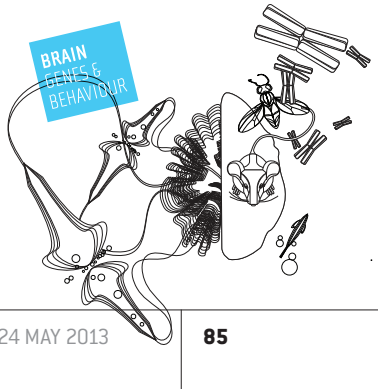
LC Schalkwyk[1], K Lunnon[1,2], R Smith[1], M Volta[1] and J Mill[1,2]

We have made a systematic, genome-wide screen for epigenetic dysfunction associated with Alzheimer's disease (AD) to uncover novel neurobiological mechanisms involved in the disease, using a unique set of highly-characterized post-mortem brain tissues, many obtained from patients who have also sequentially given blood before death.

One of the most intriguing existing observations is that there is a differential vulnerability to AD, with some regions of the brain being particularly affected and others relatively resistant. Both plaques and tangles occur first and most extensively in brain areas involved in learning and memory and emotional behaviours. Other areas such as the cerebellum, however, are relatively resistant to neuronal damage with little or no tangle formation, tau pathology or neuronal loss, even in the context of extensive plaque formation. Our genome-wide DNA methylation data on 4 brain regions and blood from 100 individuals is allowing us to model these processes and find novel genes and pathways related to the progression of the disease.

[1] MRC Social, Genetic and Developmental Psychiatry, Institute of Psychiatry, King's College London UK
[2] Medical School, University of Exeter, Exeter UK

NIH grant R01AG036039



SELECTED TALKS SESSION I

Genetic factors contributing to waiting impulsivity in mice and drug-related behaviour in human adolescents.

Yolanda Peña-Oliver[1], Sandra Sanchez-Roige[1], Stuart Rulten[2], Frances Pearl[2], Fabiana Carvalho[3], Tianye Jia [3], Gunter Schumann[3] and David N Stephens[1]

Impulsivity and compulsivity are associated with several psychiatric disorders including addiction. We used the five-choice serial reaction time task to test 10 BXD recombinant inbred (BXD RI) strains and their progenitor C57BL/6J and DBA2/J mice and seek genetic associations with "waiting impulsivity", and with unnecessary repetitive responding (a putative measure of "checking compulsivity"). Mice were trained to stable performance using a stimulus duration of 1.8s, and 5s intertrial interval (ITI), and then tested in three sessions with a long ITI of 10s to provoke high levels of premature responding. Behavioural data were correlated with genetic expression levels using GeneNetwork (www.genenetwork.org), which provides a large database of behavioural phenotypes and microarray-based gene expression data from BXD RI lines. Correlational analysis identified 42 genes whose level of expression in prefrontal cortex correlated with impulsivity with a probability exceeding a false discovery rate of <0.05, but only a single gene in accumbens. Repetitive responding was associated with expression levels of 3 genes in prefrontal cortex, and none in accumbens.
We then interrogated the IMAGEN database of 2000 human adolescents for potential genome-wide association of SNPs in those genes in the mouse study that met criterion, with smoking and alcohol experience, and impulsivity scores on the Substance Use Risk Profile Scale (SURPS). Three genes, odz4, kalrn and mbnl2 were found both to correlate with mouse impulsivity, and to be associated with frequency of drinking in the previous 30 days, binge drinking in the previous 30 days, or impulsivity scores on the SURPS.

[1] School of Psychology, University of Sussex, Falmer, Brighton BN1 9QG, UK
[2] School of Life Sciences, University of Sussex, Falmer, Brighton BN1 9QG, UK
[3] Institute of Psychiatry, Kings College, Denmark Hill, London, SE5 8AF

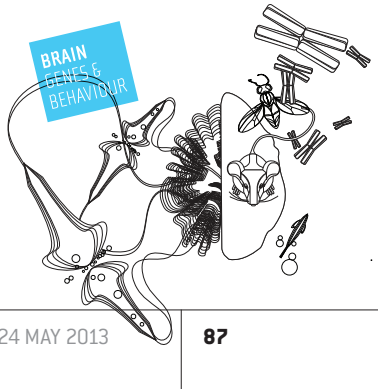
SELECTED TALKS SESSION I

Genetic and epigenetic regulation of microRNA by alcohol

A. Pietrzykowski[1], E. Mead[1], Y. Wang[1], A. Thekkumthala[1], A. Hot[1], L. Tejeda[1]

microRNAs are powerful regulators of gene expression. Previously, we showed the role of miR-9 in the development of molecular tolerance to ethanol: 15 minutes exposure to 20mM ethanol upregulated miR-9 in primary neuronal cultures. Our current observations indicate the opposite effect of chronic ethanol: miR-9 levels are decreased in saliva of chronic alcohol abusers as well as in the brain of deceased alcoholics. These observations prompted us to perform detailed temporal studies of miR-9 response to ethanol using a regimen of ethanol exposures and withdrawals ranging from 15 minutes to 24 hours of postnatal day 5 C57BL/6 mice striatal medium spiny neurons. Total RNA and small RNA (<200nt) were isolated and treated with DNase. Concentrations of mature mmu-miR-9, miR-9* and miR-9 precursors: pre-miR-9-1, -9-2, and -9-3 were determined by qRT-PCR. Surprisingly, exposure to 20 mM but not 50 mM ethanol for 15 min caused an almost 2-fold increase in miR-9 expression. Interestingly, the expression of pre-mir-9-1 was also increased in response to ethanol. Ongoing experiments analyze ethanol effect on expression of pre-miR-9-2 and -9-3 precursors. Preliminary observations indicate that longer ethanol exposures suppress levels of miR-9 in neurons. We are also currently testing interplay between genetic (SNPs) and epigenetic (DNA methylation) mechanisms on regulation of mir-9 gene expression by chronic ethanol. Sequencing of promoters of mir-9 genes in COGA samples revealed presence of several SNPs, which could alter binding of transcription factors and/or promoter methylation. These results can provide new understanding of development of alcohol addiction.

[1] Rutgers University, Department of Animal Sciences, Department of Genetics, Laboratory of Adaptation, Reward, and Addiction, 67 Poultry Farm Lane, New Brunswick, NJ 08901, USA



THURSDAY
MAY 23

SELECTED TALKS SESSION I

"Sleep stages in Drosophila"

Bruno van Swinderen[1]

Sleep in mammals is a dynamic process involving different stages of brain activity and sleep intensity. Distinct functions have been proposed for different sleep stages, including memory consolidation and synaptic homeostasis. Evidence for different sleep stages in invertebrates remains elusive, even though it has been well established that many invertebrate species require sleep. Here we show that the fruit fly, Drosophila melanogaster, transitions between deeper and lighter sleep within extended bouts of quiescence, with deeper sleep after ~12 and ~30 minutes of quiescence. As in mammals, the timing and intensity of these dynamic sleep processes in flies is homeostatically regulated and modulated by behavioral experience. Two molecules linked to synaptic plasticity regulate the intensity of the first deep sleep stage. Optogenetic up-regulation of cyclic adenosine monophosphate (cAMP) increases sleep intensity, whereas expression of a molecule involved in synaptic pruning, the fragile-X mental retardation protein (FMRP), has the opposite effect. Our behavioral and electrophysiological results show that sleep is a dynamic process in insects, and suggest that waking behavior and associated synaptic plasticity mechanisms determine the timing and intensity of deep sleep stages in Drosophila.

[1] Queensland Brain Institute, The University of Queensland, Brisbane, 4072 , Queensland, Australia

Support: ARC (Australia), NIH (USA)

SELECTED TALKS SESSION I

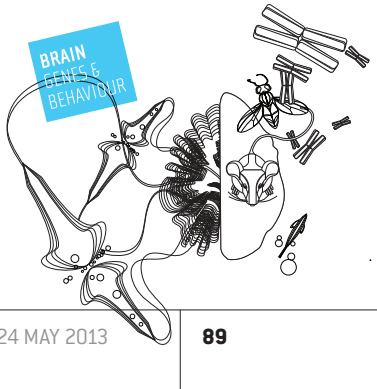
Yueju pill rapidly triggers antidepressant-like effects

Wenda Xue[1,2], Xin Zhou[1,2,3], Nan Yi[4], Lihua Jiang[5], Haoxin Wu[1,2,] Gang Chen [1,2]

Current monoamine-based antidepressants have a major drawback of several-weeks-long lag period of therapeutic efficacy. The faster-acting antidepressant is needed, particularly for suicide-risking patients. Although ketamine is an emerging antidepressant to act fast and last long, there are concerns of adverse behavioral effects and abuse potential. Several clinical outcome reports have indicated a relative short onset of antidepressant effect of a classic herb medicine, Yueju, prompting us to examine the effects using animal models and study underlying molecular mechanisms. Using the outbred strain Kunming mice, we found as fast as 24 hours post an acute administration of the Yueju ethanol extract, depressive-like behavior in the learned helplessness paradigm were attenuated. An acute administration of Yueju also significantly reduced novelty suppressed feeding. Both effects require a few days long administrations of monoamine-based antidepressants. Furthermore, the antidepressant-like effects sustained for 7 days in the tail suspension test. Interestingly, Yueju, like ketamine, rapidly increased the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, whereas the Bdnf mRNA expression remained unaltered. Yuejue likely enhanced BDNF protein expression via posttranscriptional regulation, as it rapidly downregulated eukaryotic elongation factor 2 (eEF2) phosphorylation that suppresses BDNF synthesis. Yueju pill has been formulated for eight hundred years and still popularly prescribed in China for alleviation of depression-like symptoms without notable side effects. Our study is the first to demonstrate the ketamine-like antidepressant effects of Yueju, offering a new opportunity to improve therapeutic efficacy on depression.

[1] Center for Translational Systems Biology and Neuroscience
[2] Key Laboratory of Integrative Ressearch on Brain Disorders
[3] TCM Jingui Research Section, School of Basic Biomedical Science, Nanjing University of Chinese Medicine, Nanjing, China, 210023
[4] School of Life Science, Nanjing Normal University, Nanjing, China, 210023
[5] Medical School, Jinan University, Guangzhou, China, 510632

Support: JiangSu Specially-Appointed Faculty Plan Fund, China



THURSDAY
MAY 23

SELECTED TALKS SESSION I

Synaptoneurosome mRNA and microRNA: Regulation by Chronic Alcohol Consumption

D. Most[1,2], R.D. Mayfield[1], Y.A. Blednov[1], R.A. Harris[1,2]

Alcohol dependence is tightly linked to changes in gene expression. MicroRNAs are a class of RNAs that have been found to regulate gene expression and translation into protein, enabling them to affect many gene networks simultaneously. The extensive synaptic plasticity associated with alcohol dependence relies on many mRNAs, which are controlled by specific microRNAs. microRNAs regulate local translation of mRNA into protein in synaptic compartments of the cell.
To test the hypothesis that specific mRNA-microRNA changes are the result of chronic alcohol use, we used an alcohol drinking paradigm (one month continuous two-bottle choice with 20% ethanol in C57Bl/6J female mice). Expression profiling of the microRNAs and mRNAs was done using preparations enriched with synaptoneurosomes using mRNA and microRNA microarrays and samples from the amygdala. The alcohol responsive mRNAs (mRNAs with more than 10% fold change due to ethanol treatment) revealed 710 up-regulated and 413 down-regulated in the synaptoneurosome preparation, whereas the total homogenate only detected 96 up-regulated and 64 down-regulated. The mRNAs found significantly different between treatment and control in the synaptoneurosome preparation were 1,531 whereas in the total homogenate only 462 were detected, suggesting that the synaptoneurosome preparation can identify a greater number of significantly changed genes. Weighted correlation network analysis (WGCNA) and multiple Pathway analyses such as Ingenuity, KEGG and Gene Ontology were used and revealed extensive modulation of many important pathways, emphasizing the usefulness of the synaptoneurosome preparation to define gene targets that may be used for therapy of alcohol dependence.

[1] Waggoner Center for Alcohol & Addiction Research
[2] The Institute for Neuroscience, The University of Texas at Austin, TX 78712

Funding Support: NIAAA grants AA012404 and AA020683

THURSDAY
MAY 23

GENERAL BUSINESS MEETING

All participants are welcome

BANQUET

Faculty Club Infirmerie

SELECTED TALKS SESSION II

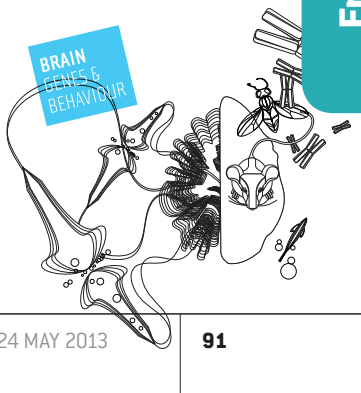
An RNA-Seq approach identifies functional networks controled by the neuronal ELAV/Hu RNA-binding proteins

X Sun[1], D Zanini[1], D Sturgill[2], J-M Jallon[1], B Oliver[2], L Rabinow[1], M-L Samson[1]

The fne (found-in-neurons) locus encodes one of the three paralogs of the ELAV gene family of Drosophila melanogaster (with elav and rbp9). Members of this family are found throughout metazoans and encode RNA-binding proteins with primarily neuronal localization. These proteins regulate gene expression at the post-transcriptional level, by modulating RNA processing, half life, transport or translation. We generated fnenull mutations by targeted homologous recombination. In contrast to elav and similar to rbp9, fnenull mutants are viable, but exhibit a specific and fully penetrant fusion of the beta-lobes in their mushroom bodies. We found that mutant males have reduced courtship indices but normal short and long term courtship memory.
We used RNA-Seq, a quantitative method of high throughput sequencing of non-cloned cDNA libraries, to compare the transcriptomes of normal and fne- Drosophila in order to identify functional networks controled by FNE. So far, our analysis focused on the regulation of stable transcript levels (Cufflinks and Cufflinks) and alternative splicing of transcripts (using Spanki, a sofware package that we developped, Sturgill et al., submitted). Only about 40 genes have been identified and validated as fne targets so far. A gene ontology (GO analysis) shows a significant enrichment for genes involved in synaptic transmission, neurotransmitter secretion and synaptic vesicule exocytosis. We have already obtained preliminary data revealing genetic interactions between the fne mutation and another viable mutation altering the synaptic terminal, where neurotransmission occurs.

[1] Centre de Neurosciences Paris-Sud UMR 8195, CNRS/Univ. Paris Sud, Orsay F-91405 CEDEX France
[2] National Institutes of Health NIDDK, Building 50, Bethesda, MD 20892, USA

Funding Support: CNRS (FRANCE), University of Paris Sud (FRANCE), NIH (USA), Chinese Scholarship Council (CHINA)



FRIDAY
MAY 23

SELECTED TALKS SESSION II

Zebrafish Genome Editing Using Random and Targeted Engineering Approaches For Bahavioral and Addiction Genetics Applications

Alvin C Ma[1], Jarryd M Campbell[1], Margot Cousin[1], Victoria M Bedell[1], Kevin L Neff[1], David P Argue[1], Karl J Clark[1], and Stephen C Ekker[1]

The zebrafish has the potential for diverse genetic and behavioral studies conducted within the biological framework of a vertebrate. We have engineered transposon tools including protein trap gene- breaking vectors for the zebrafish. We are generating a random collection of molecularly characterized and revertible mutant zebrafish lines at the Mayo Clinic and in collaboration with labs around the world as a part of the International Protein Trap Consortium. These molecularly tagged, revertible and readily genotyped lines are ideally suited to the genetic study of neuroscience including behavior and addiction. We currently have over 500 lines, with 500+ more in process (up-to-date info at zfishbook.org). Maximal use of these and related revertible alleles by the zebrafish community will require a set of well- described tissue-specific Cre lines.
Custom restriction endonucleases offer a complementary approach, targeted genome modification. We have used the highly active GoldyTALEN system to conduct genome editing applications in zebrafish, including the introduction of small engineered changes suitable for modeling human disease using the zebrafish. We have also successfully introduced specific loxP sequences for gene switch applications in our favorite model system. We have generated a web-based TALEN design software (talendesign.org) as well as a followup Golden Gate TALEN assembly toolbox to support access to these reagents by the scientific community. We are deploying these highly active tools for the generation of targeted larger genomic deletions using two TALEN pairs, and we are optimizing protocols for epitome-tagging loci including the nicotine receptor family in zebrafish. This targeted genome editing system opens the door to an array of new genetic methods for exploring addiction and behavioral science.

[1] Department of Biochemistry and Molecular Biology and the Mayo Addiction Research Center, Mayo Clinic., Rochester, MN USA

Funding Support: NIH GM63904; DA14546; P30DK084567; State of Minnesota and Mayo Foundation

SELECTED TALKS SESSION II

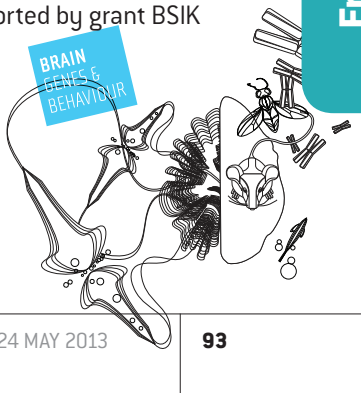
High throughput phenotyping of spontaneous behavior: variation within and across 11 inbred mouse strains

Maarten Loos[1,2]‡, Bastijn Koopmans[1]‡, Emmeke Aarts[3], Gregoire Maroteaux[3], Sophie van der Sluis[3,4], Neuro-BSIK Mouse Phenomics consortium[5], Matthijs Verhage[3,4]‡, August B. Smit[2]‡

Functional genetic analyses, gene finding and pharmacological studies in mice require in-depth knowledge of the behavioral spectrum of the background strains used. We systematically analyzed and compared spontaneous behavior of a panel of commonly used inbred strains (129S1/SvImJ, A/J, C3H/HeJ, C57BL/6J, BALB/cJ, DBA/2J, NOD/LtJ, FVB/NJ, WSB/EiJ, PWK/PhJ and CAST/EiJ) by high-throughput automated home cage observation. Continuous video-tracking observations were segmented into distinguishable behavioral elements, and studied at different time scales, yielding a multivariate set of 115 behavioral parameters of which 105 showed highly significant strain differences. Especially BALB/c, FVB/NJ and C3H/HeJ mice provided extreme values (on 17, 15 and 13 % of the parameters, respectively), whereas C57BL/6J mice showed extreme values on only few parameters (4 %), including habituation, anticipation of the dark phase and maximum velocity. C57BL/6J and BALB/c mice ranked lowest in terms of within-strain variation, especially in comparison to the highly variable 129S1/Sv and DBA/2J strains.
Thus, the C57BL/6J strain is optimal for genetic intervention and pharmacological studies because it shows (i) few extreme values, hence, facilitates detection of both upward and downward phenotypic changes and (ii) low within-strain variation, increasing the statistical power to detect intervention effects. In conclusion, this study shows that genetic background strongly influences spontaneous home cage behavior, and it provides a reference dataset for genetic and pharmacological studies of mouse behavior in the home cage.

[1] Sylics (Synaptologics BV), Amsterdam, The Netherlands
[2] Department of Molecular and Cellular Neurobiology
[3] Department of Functional Genomics, Center for Neurogenomics and Cognitive Research (CNCR), Neuroscience Campus Amsterdam, VU University Amsterdam
[4] Department of Clinical Genetics, VU Medical Center, Amsterdam, The Netherlands and 5 Collaborators: Brussaard AB, Borst JGG, Elgersma Y, Galjart N, van der Horst GT, Levelt CN, Pennartz CM, Smit AB, Spruijt BM, Verhage M, de Zeeuw CI
‡These authors contributed equally to this work.

Support:
S. van der Sluis was financially supported by NWO/MaGW VENI-451-08-025.
This study was in part funded by the Dutch Neuro-Bsik Mouse Phenomics consortium, supported by grant BSIK 03053 from SenterNovem (The Netherlands).



FRIDAY
MAY 23

SELECTED TALKS SESSION II

Bidirectional change of maturation status of dentate gyrus neurons: Relevance to neuropsychiatric disorders.

Tsuyoshi Miyakawa[1], Keizo Takao[1], Koji Ohira[1], Hideo Hagihara[1]

Adequate maturation and integration of the adult-generated neurons into the circuit of the hippocampus would be crucial for normal cognitive functions and emotional behaviors. Disruption of the process could result in some disturbance in mental health. Previously, we reported that mice heterozygous for a null mutation of αCaMKII, a key molecule in synaptic plasticity, have profoundly dysregulated behaviors including hyper-locomotor activity and a severe working memory deficit, which are endophenotypes of schizophrenia and other psychiatric disorders. In these mice, almost all the neurons in the dentate gyrus (DG) of the mutant mice failed to mature at molecular, morphological and electrophysiological levels, causing severe deficit in the synaptic plasticity at mossy fiber – CA3 synapses. By using a simple real-time PCR assay using iDG markers, we identified four other strains of mutant mice that have a phenotype strikingly similar to iDG, including the forebrain specific calcineurin knockout mice and the mice lacking a transcription factor, schnurri-2. We also found that chronic fluoxetine treatment or single pilocarpine administration can induce "dematuration" resulting in iDG-like phenotype in wild type mice. Most of the mice showing iDG-like phenotype seem to have increased adult neurogenesis in DG. Gene and protein expression patterns in the brains of these mice are similar to those found in the post-mortem brains of the patients of psychiatric disorders, such as schizophrenia and bipolar disorder. Interestingly, the brains of such iDG mice show mild chronic inflammation, which is distinct from typical acute inflammation. Anti-inflammatory drugs can reverse the iDG phenotype as well as some behavioral abnormalities in a subset of the mice showing iDG. We discuss the potential implication of these findings in elucidating the pathophysiology of those neuropsychiatric disorders.

[1] Division of Systems Medical Science, Fujita Health University, Japan

Funding: CREST, JST and KAKENHI, MEXT

SELECTED TALKS SESSION II

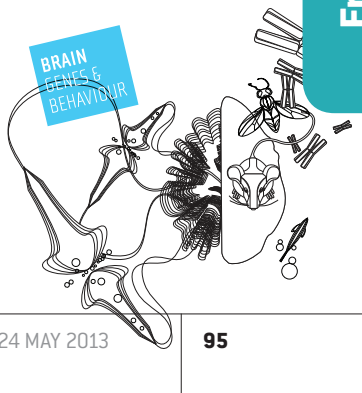
The increased release of Biogenic Amines is responsible for behavioral effects of Nicotine, MTA and MDMA in Drosophila melanogaster.

Campusano JM[1], Escobedo P[1], Fuenzalida-Uribe N[1], Varas R[1].

Nicotine, MDMA (3,4-methylenedioxymethamphetamine) and MTA (4- Methylthioamphetamine) are drugs that pose a major health problem worldwide, involved in addiction, severe damage and even death. Numerous evidences have shown that the biological effects of these compounds depend on Biogenic Amine (BA) systems (e.g. dopamine serotonin, etc.) that are highly conserved from invertebrates to higher mammals. It is known that in vertebrates the effects of nicotine and MDMA and MTA depend on the activation of nicotinic acetylcholine receptors (nAChRs) and the synaptic transporters for BAs, which regulate the release of BAs.
Invertebrates exposed to drugs of abuse display a set of behaviors including increased locomotion, stereotypy and behavioral sensitization, as shown in vertebrates. However, it is not known whether the effect of these drugs depend on the modulation of the activity of BA systems in invertebrate systems.
Here, by using a chronoamperometric setup and different genetic tools available in the fly Drosophila melanogaster, we show that nicotine, MTA and MDMA induce the release of endogenous BAs in the fly brain. We further show that the increased release of endogenous BAs is responsible for the behavioral effects induced by these drugs.

[1] Laboratorio de Neurogenética de la Conducta, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, CHILE. jcampusano@bio.puc.cl

Supported by Fondecyt 1100965, VRI-PUC 39-2011, MSI 10-063-F



FRIDAY
MAY 23

SELECTED TALKS SESSION II

The effect of the 5-HTTLPR polymorphism on face emotion recognition in schizophrenia

MV Alfimova[1], VE Golimbet[1], GI Korovaitseva[1], LI Abramova[1], EV Aksenova[1], MI Bolgov[2], TK Ganisheva[2]

Neuroimaging studies have revealed main and interaction effects of the serotonin transporter (5-HTT) and catechol-O-methyltransferase (COMT) genes on brain activity during processing of facial emotion information in healthy subjects and in a number of psychiatric conditions. We aimed to extend these findings by studying main and interaction effects of these genes on a performance measure of facial emotion recognition in schizophrenia. 497 schizophrenic patients and 240 healthy controls passed experimental examination which included the task of labeling facial expressions of nine emotions. Of those 430 patients and 197 controls were genotyped for the COMT Val158Met polymorphism and 299 patients and 231 controls for the 5HTTLPR one. The patients performed the emotion recognition task poorer than the controls. Controlling for sex and age we found significant effects of the 5HTTLPR polymorphism and its interaction with group on emotion recognition with LL homozygotes overperforming those with LS and SS genotypes. The gene effect was significant solely in the patients group. Moreover, the emotion recognition deficit of schizophrenics was correlated with PANSS negative symptom scores, anxiety (STAI), verbal memory (RAVLT) and executive function (TMT-B, verbal fluency) variables. The 5HTTLPR effect on emotion recognition remained highly significant when adjusting for the aforementioned clinical, anxiety and neurocognitive measures. Neither COMT nor COMTx5HTTLPR effect reached the level of significance. The results suggest that in schizophrenia the 5HTTLPR S allele impacts the facial emotion recognition deficit, irrespective of anxiety, symptoms and basic cognitive processes.

[1]Mental Health Research Center of RAMS
[2]Psychiatric Clinical Hospital N 1, Moscow, Russia

Funding Support: Grant 12-06-00040a of the Russian Foundation for Basic Research, MHRC RAMS, RUSSIA

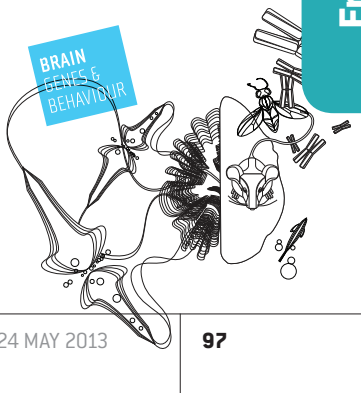
SELECTED TALKS SESSION II

Dopamine in Sexual Behavior

J. Lim[1], A. Smith[1], A. Nava[1] and K.-A. Han[1]

Dopamine is involved in reward, motivation, reinforcement, movement, learning and memory. By using a powerful genetic model Drosophila melanogaster, we aim to dissect the mechanisms by which dopamine mediates diverse brain functions. For this task, we employ a conditioned courtship paradigm, in which a male fly's courtship behavior is modified by persistent rejection of a mated female. The rejected male fly learns to associate unsuccessful courtship and copulation with the female fly and displays a generalized aversion (via courtship suppression) toward a virgin female. We tested the flies lacking D1 receptor dDA1 (dumb1 and dumb2), D2 receptor dDR2 (dd2r), dopamine/steroid ecdysone receptor DopEcR (der), D5 receptor DAMB (damb), and dopamine transporter DAT (fmnroo and fmnZuker). While all mutants exhibited normal learning in conditioned courtship suppression, we found an intriguing defect on courtship motivation in dumb, but not the other, mutant males. Studies are in progress to map the neural site that D1 receptor plays a role in sexual motivation.

[1] Department of Biological Sciences, BBRC Neuroscience/Metabolic Disorders, University of Texas at El Paso, El Paso, TX USA



FRIDAY
MAY 23

SYMPOSIUM VI

EPIGENETICS OF BRAIN DISORDERS: FOCUS ON ALCOHOLISM

CHAIR: IGOR PONOMAREV
ANTONIO NORONHA

ALFREDO GHEZZI
Epigenetic modulation of long-term neural adaptations that underlie alcohol tolerance and dependence in Drosophila

MICKAEL NAASSILA
Is there a future for using HDAC inhibitors in alcohol dependence?

GEORGY BAKALKIN
Mechanistic integration of the genetic, epigenetic and environmental factors in neuropsychiatric diseases: Analysis of opioid genes in human alcoholism

TOMAS EKSTRÖM
The functional genome at the genetic-epigenetic-environment intersection

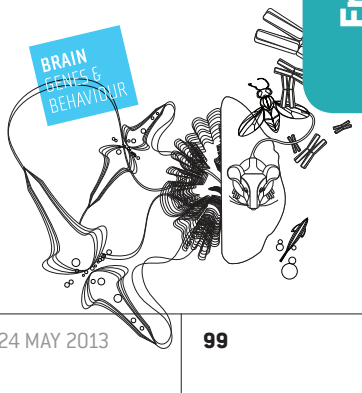
FRIDAY
MAY 23

Epigenetic modulation of long-term neural adaptations that underlie alcohol tolerance and dependence in Drosophila

Alfredo Ghezzi, Xiaolei Li, Harish Krishnan, Brooks Robinson, Linda Lew, and Nigel S. Atkinson

Sustained or repeated exposure to sedating drugs such as alcohol and anesthetics triggers homeostatic adaptations in the brain that lead to the development of drug tolerance and dependence. Adaptation to addictive drugs appear to involve long-term changes in the transcriptional activity of drug-responsive genes as well as an epigenetic restructuring of chromosomal regions to signal and maintain the altered transcriptional state. For instance, alcohol-induced changes in histone acetylation have been shown to trigger changes in neurons that lead to the alcoholism endophenotypes of tolerance and dependence. These changes are believed to be of central importance in producing the addictive state. Here, we use Drosophila to explore the mechanisms behind the epigenetic modifications underlying alcohol tolerance. Through a combination of genome-wide surveys of alcohol-induced histone modifications and behavioral analysis of mutant and RNAi lines, we have identified a network of genes with roles in the modulation of neural activity that are essential for the development of alcohol tolerance. Furthermore, we find that the Drosophila histone-acetyl transferase CBP, contributes to the epigenetic regulation during the development of tolerance to alcohol. Through this approach, we have begun to decipher the overarching transcriptional events orchestrating the adaptations that contribute to alcohol addiction.

[1] Section of Neurobiology and Waggoner Center for alcohol and Addiction Research, The University of Texas at Austin. Austin, Texas, USA



FRIDAY
MAY 23

Is there a future for using HDAC inhibitors in alcohol dependence?

E Simon O'Brien [1], V Warnault [2], Rémi Legastelois [2], Béatrice Botia [1], C Vilpoux [1], S Alaux-Cantin [1], O. Pierrefiche [1], M. Naassila 1

Emerging evidence suggests that epigenetic alterations to the genome, including DNA methylation and histone modifications, are important mechanisms underlying alcohol addiction. With the new field of epigenetics, there is now the opportunity to integrate the role of the epigenome not only in the short-term effects of alcohol but also in the enduring neuro-adaptations caused by chronic use of alcohol. The epigenetic modifications may be part of the neuro-adpatations occurring during the transition from the controlled intake to the loss of control and may explain how alcohol can have such a persistent effect on brain gene expression and functioning. There are now accumulating data showing that pharmacological tools targeting enzymes involved in epigenetic modifications may be useful in reducing or preventing some behavioral responses to alcohol. In the present work we have investigated the effects of different HDAC inhibitors (sodium butyrate, trichostatine A, MS-275 and sirtinol) on alcohol intake in rats with several paradigms, i.e. operant 10% ethanol self-administration, intermittent 20% ethanol intake and alcohol deprivation effect. We have also investigated the effects of HDAC inhibitors on excessive alcohol intake in alcohol-dependent animals and explored associated modifications in the brain levels of acetylated histone H3. Finally we tested the effects of HDAC inhibitors on ethanol-induced behavioral locomotor sensitization in mice and analyzed alterations in striatal gene expression and both HDAC and HAT activities. Altogether our results show that HDAC inhibitor can reduce and / or prevent several behavioral effects of alcohol and that this effect of HDAC inhibitors can be due, at least in part, to epigenetic mechanism.

[1] Research Group on Alcohol & Pharmacodependences (GRAP), Inserm Unit Eri 24, University of Picardie Jules Verne, Amiens, France
[2] Ernest Gallo Center, 5858 Horton Street, Suite 200, Emeryville, CA 94608

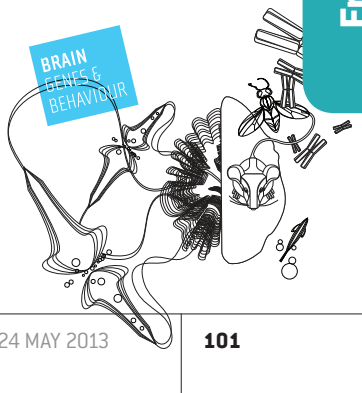
FRIDAY
MAY 23

Mechanistic integration of the genetic, epigenetic and environmental factors in neuropsychiatric diseases: Analysis of opioid genes in human alcoholism

G. Bakalkin, I. Bazov, M.M.H. Taqi, H. Watanabe, O. Kononenko, I. Bazov and T. Yakovleva

Expression of the genome may be influenced by the environment by shaping epigenetic mechanisms. Mechanistically, effects of genetic, epigenetic and environmental factors may converge on SNPs that reside in CpG dinucleotides and thus represent methylation associated SNPs (methSNPs). The resulting methSNP methylation signals may be translated into predisposition to develop a disease through their effects on gene expression. The average occurrence rate of SNPs at a CpG site is ten-fold higher than the overall SNP occurrence rate, thus methSNPs are overrepresented in the human genome (Xie et al., 2009). Analysis of the correlation of methylation between CpG methylation and SNPs identified allele specific methylation (ASM) on app. 30% heterozygous SNPs, and found that a significant fraction, up to
88% of ASM regions is dependent on the presence of methSNPs (Shoemaker et al., 2010). The methSNP hypothesis received support in recent studies by us and others (John et al., 2011; Kaminsky et al., 2011; Martin-Trujillo et al., 2011; Reynard et al., 2011; Taqi et al., 2011; Ursini et al., 2011). We addressed this hypothesis by analyzing methylation of the prodynorphin gene (PDYN) methSNPs associated with alcohol dependence. Expression of PDYN producing opioid peptides dynorphins was found to be elevated in the dorsolateral prefrontal cortex (dl-PFC) of human alcohol-dependent subjects. Three PDYN methSNPs associated with alcoholism were found to be differentially methylated in human brain. In the dl-PFC of alcoholics, methylation levels of the C, non-risk variant of 3´-untranslated region (3´-UTR) SNP (rs2235749) were increased, and correlated with PDYN mRNA and dynorphins. A DNA-binding factor that differentially targeted the T, risk allele and methylated and unmethylated C allele of this SNP was identified in brain. These findings suggest a causal link between alcohol-associated PDYN 3´-UTR methSNP methylation, activation of PDYN transcription, and vulnerability to develop alcohol dependence.

[1] Dept. Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.



FRIDAY
MAY 23

The functional genome at the genetic-epigenetic-environment intersection

Tomas Ekström[1]

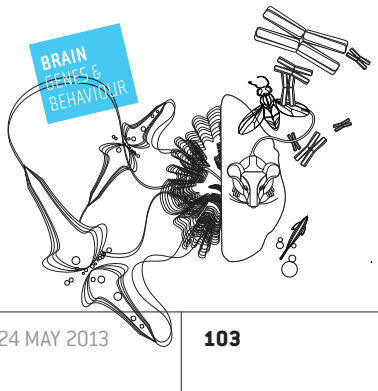
With the rapidly increasing insights into basic mechanisms of epigenetics, it is now becoming possible to understand the more precise mechanisms whereby environment and life style influence disease development. Alterations in the epigenetic states, i.e. in DNA-methylation, and nucleosomal histone modifications, result in changes of gene expression and are instrumental for regulating specific gene programs and phenotypes, including those of diseases. We have addressed the epigenetic/phenotype intersection in two psychiatric conditions, schizophrenia and chronic alcoholism, by analyzing DNA-methylation alterations. In the chronic alcoholic prefrontal cortex we identified alterations in genes known to be involved in an inheritable autosomal syndrome with similar phenotype as found in alcoholics. In peripheral blood leukocytes from schizophrenia patients we found evidence for patient global and gene-specific DNA-methylation alterations that was dependent on disease onset and therapy type. Studies of epigenetics are also needed in order to understand the impact of the classic genetic variations that have recently been captured from genome-wide studies of complex genetic disease. The integrations between the genome and epigenome, and their interdependence with environmental impact, for disease phenotype are of obvious importance. The dependence of the genetic background for the dynamic epigenome, is previously shown by our findings that there are obvious familial predisposition for epigenetic variation. Our recent results further suggest that integrated genetic and epigenetic analyses enhance the resolution of information, so that it is possible to identify genetic risk alleles for disease that would otherwise be opaque to conventional analysis due to sample size limitations. By using a causal inference testing algorithm with genetic, epigenetic, and phenotypic data, we show a dependence on DNA methylation for the penetrance of several risk alleles in rheumatoid arthritis, suggesting DNA methylation as a mediator of genetic risk for disease.

[1] Medical Epigenetics Unit, Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

TRAVEL AWARDEES

Applicant's Name	Affiliation	Country
Graduate Students		
Barkley-Levenson Amanda	Oregon Health & Science University	USA
Bühler Kora-Mareen	Complutense University of Madrid	Spain
Cousin Margot	Mayo Clinic	USA
Darlington Todd	University of Colorado	USA
Eastwood Emily	Oregon Health & Science University	USA
Fraser Leanne	Dalhousie University	Canada
Fritz Brandon	Indiana Univ Purdue Univ – Indianapolis	USA
Fuenzalida (Uribe) Nicolás	Catholic University of Chile	Chile
Harkness John	Oregon Health & Science University	USA
Janecka Magdalena	King's College London	UK
Kasten Chelsea	Indiana Univ Purdue Univ – Indianapolis	USA
Liang Zhengzheng *	University of Illinois	USA
Majdak Petra	University of Illinois	USA
Malan-Müller Stefanie	Stellenbosch University	South Africa
Mehta Neha	Northwestern University	USA
Melroy Whitney	University of Colorado	USA
Michetti Caterina	Sapienza University, Rome	Italy
Mitchnick Krista *	University of Guelph	Canada
Most Dana	University of Texas at Austin	USA
Mustroph Martina	University of Illinois	USA
Naik Roshan	Max Planck Institute of Psychiatry, Munich	Germany
Palmer Daniel	University of Guelph	Canada
Romano Emilia	Sapienza University, Rome	Italy
Postdoc Trainees		
Linsenbardt David *	Indiana Univ Purdue Univ – Indianapolis	USA
Gallego Xavier	University of Colorado	USA
Junior Faculty		
Bryant Camron *	Boston University	USA
Campusano Jorge	Catholic University of Chile	Chile
Clark Karl	Mayo Clinic	USA
Ghezzi Alfredo	University of Texas at Austin	USA
Kliethermes Christopher	Drake University	USA
Syed Sheyum	University of Miami	USA

** 2013 Outstanding Travel Awardees*



PARTICIPANT LIST

Name	First Name	University/Institution	Email
Alfimova	Margarita	Mental Health Research Center of RAMS	m.alfimova@gmail.com
Atkinson	Nigel	The University of Texas at Austin	nsatkinson@austin.utexas.edu
Baier	Herwig	MPI of Neurobiology	cerny@neuro.mpg.de
Bakalkin	Georgy	Uppsala University	Georgy.Bakalkin@farmbio.uu.se
Barkley-Levenson	Amanda	Oregon Health & Science University	barkleya@ohsu.edu
Blomqvist	Anders	Linköping University	anders.blomqvist@liu.se
Boehm	Stephen	Indiana University - Purdue University Indianapolis	slboehm@iupui.edu
Brennan	Caroline	Queen Mary University of London	c.h.brennan@qmul.ac.uk
Brown	Richard E.	Dalhousie University	rebrown@dal.ca
Bryan	Angela	University of Colorado Boulder	angela.bryan@colorado.edu
Bryant	Camron	Boston University School of Medicine	camron@bu.edu
Bubier	Jason	The Jackson Laboratory	jbubier@jax.org
Bûhler	Kora-Mareen	Complutense University Madrid	kobuhler@psi.ucm.es
Campusano	Jorge	Pontificia Universidad Catolica de Chile	jcampusano@bio.puc.cl
Caruso	Angela	Istituto Superiore di Sanità	angyca@live.it
Chen	Gang	Nanjing University of Chinese Medicine	hdn_2001@yahoo.com
Chesler	Elissa	The Jackson Laboratory	elissa.chesler@jax.org
Clark	Karl	Mayo Clinic	clark.karl@mayo.edu
Cousin	Margot	Mayo Clinic	cousin.margot@mayo.edu
Crabbe	John	VA Medical Center	crabbe@ohsu.edu
Crusio	Wim E.	University of Bordeaux and CNRS	wim_crusio@yahoo.com
Czibere	Ludwig	MPI of Psychiatry	czibere@mpipsykl.mpg.de
Darlington	Todd	University of Colorado	todd.darlington@colorado.edu
Dubnau	Josh	Cold Spring Harbor Laboratory	dubnau@cshl.edu
Dulawa	Stephanie	University of Chicago	dulawa@uchicago.edu
Eastwood	Emily	Oregon Health & Science University	eastwooe@ohsu.edu
Echeverry Alzate	Víctor	Complutense University of Madrid	echeverry.v@psi.ucm.es
Ehringer	Marissa	University of Colorado	Marissa.Ehringer@colorado.edu
Ekker	Stephen	Mayo Clinic	ekker.stephen@mayo.edu
Ekstr√∂m	Tomas	Karolinska Institutet	tomas.ekstrom@ki.se
Emilsson	Lina	Uppsala University	lina.emilsson@ebc.uu.se
Enoch	Mary-Anne	NIAAA, NIH	maenoch@niaaa.nih.gov
Fernandes	Cathy	Institute of Psychiatry	catherine.fernandes@kcl.ac.uk
Filali	Mohammed	Laval University/CHUQ	Mohammed.Filali@crchul.ulaval.ca
Fraser	Leanne	Dalhousie University	leanne.fraser@dal.ca
Fritz	Brandon	Indiana University-Purdue University Indianapolis	bmfritz@iupui.edu
Fuenzalida	Nicolas	Catholic University of Chile	nlfuenzalida.u@gmail.com
Gallego	Xavier	University of Colorado Boulder	francesc.gallegomoreno@colorado.edu
Gerlai	Robert	University of Toronto Mississauga	robert_gerlai@yahoo.com
Ghezzi	Alfredo	University of Texas at Austin	aghezzi@utexas.edu
Gine	Elena	UNIVERSIDAD COMPLUTENSE DE MADRID	elena.gine@med.ucm.es
Gyekis	Joseph	Penn State University	jgyekis@yahoo.com
Han	Kyung-An	University of Texas at El Paso	khan@utep.edu
Harkness	John	Oregon Health & Science University	harknesj@ohsu.edu
Herz	Joachim	UT Southwestern Medical Center	joachim.herz@utsouthwestern.edu
Homberg	Judith	Radboud University Nijmegen Medical Centre	j.homberg@cns.umcn.nl
Hovatta	Iiris	University of Helsinki	iiris.hovatta@helsinki.fi
Hutchison	Kent	University of Colorado Boulder	kent.hutchison@colorado.edu
Iakovleva	Tatiana	Uppsala University	tatiana.iakovleva@farmbio.uu.se
Janecka	Magdalena	King's College London	magdalena.janecka@kcl.ac.uk
Janus	Christopher	University of Florida	janus.christopher@gmail.com
Jazin	Elena	Uppsala University	elena.jazin@ebc.uu.se
Johansson	Martin	Uppsala University - Evolutionary Biology Centre	ros-marina@o2.pl
Kasten	Chelsea	Indiana University Purdue University - Indianapolis	ckasten@iupui.edu
Kilby	Chessa	University of Illinois	kilby1@illinois.edu
King	Andrea	University of Chicago	aking@bsd.uchicago.edu
Kliethermes	Christopher	Drake University	c.kliethermes@drake.edu
Koks	Sulev	University of Tartu	Sulev.Koks@ut.ee

PARTICIPANT LIST

Name	First Name	University/Institution	Email
Koks	Sulev	University of Tartu	Sulev.Koks@ut.ee
Kulesskaya	Natalia	University of Helsinki	natalia.kulesskaya@helsinki.fi
Kyriacou	Charalambos	University of Leicester	cpk@leicester.ac.uk
Lewejohann	Lars	University of Muenster	ljohann@phenotyping.com
Li	Wanhe	The Rockefeller University	wli02@rockefeller.edu
Liang	Zhengzheng	University of Illinois at Urbana-Champaign	zliang2@life.illinois.edu
Liao	Yung-Feng	Academia Sinica	yliao@sinica.edu.tw
Liedvogel	Miriam	Lund University	miriam.liedvogel@biol.lu.se
Linsenbardt	David	IUPUI	dlinsenb@iupui.edu
Lipp	Hans-Peter	University of Zurich	hplipp@anatom.uzh.ch
Loos	Maarten	Sylics (Synaptologics B.V.)	maarten.loos@sylics.com
LOPEZ-MORENO	JOSE ANTONIO	COMPLUTENSE UNIVERSITY OF MADRID	jalopezm@psi.ucm.es
Lyon	Gholson	Cold Spring Harbor Laboratory	apotopsi@cshl.edu
Madani	Rime	AC Immune SA	erika.menamkat@acimmune.com
Majdak	Petra	UIUC	petra.majdak@gmail.com
Malan-Mûller	Stefanie	Stellenbosch University	smalan@sun.ac.za
Mehta	Neha	Northwestern University	nsmehta@u.northwestern.edu
Melroy	Whitney	University of Colorado Boulder	whitney.melroy@colorado.edu
Mets	David	University of California, San Francisco	dmets@phy.ucsf.edu
Meyer-Lindenberg	Andreas	Central Institute of Mental Health in Mannheim	a.meyer-lindenberg@zi-mannheim.de
Michetti	Caterina	Istituto Superiore di Sanità	caterinamichetti@hotmail.com
Mitchnick	Krista	University of Guelph	kmitchni@uoguelph.ca
Miyakawa	Tsuyoshi	Fujita Health University	miyakawa@fujita-hu.ac.jp
Most	Dana	University of Texas at Austin	danamost@gmail.com
Mulligan	Megan	UTHSC	mulliganmk@gmail.com
Mustroph	Martina	University of Illinois	mmustr2@illinois.edu
NAASSILA	Mickael	Université de Picardie Jules Verne	mickael.naassila@u-picardie.fr
Naik	Roshan	Max Planck Institute of Psychiatry	naik@mpipsykl.mpg.de
Nava	Anne	University of Texas at El Paso	aknava@miners.utep.edu
Nicod	Jerome	Oxford University	nicod@well.ox.ac.uk
Noronha	Antonio	NIAAA	Helen.Kamens@colorado.edu
Oliveira	Rui	ISPA	ruiol@ispa.pt
Ophir	Galit	Janelia Farm Research Campus	ophir.galit@gmail.com
Palmer	Abraham	University of Chicago	aap@uchicago.edu
Palmer	Daniel	University of Guelph	dpalmer@uoguelph.ca
Phillips	Tamara	Oregon Health & Science University	phillipt@ohsu.edu
Pietrzykowski	Andre	Rutgers University	andrepi@aesop.rutgers.edu
Ponomarev	Igor	University of Texas at Austin	ponomarev@utexas.edu
Quoilin	Caroline	Indianapolis University-Perdue	cquoilin@iupui.edu
Radcliffe	Richard	University of Colorado	richard.radcliffe@ucdenver.edu
Roelofs	Reinko	Noldus IT	r.roelofs@noldus.nl
Romano	Emilia	Istituto Superiore di Sanità	emilia.romano@iss.it
Rutledge-Gorman	Mark	Oregon Health & Science University	rutledgm@ohsu.edu
Samson	Marie-Laure	CNRS UMR 8195 Universite Paris Sud	Marie-Laure.Samson@u-psud.fr
Schalkwyk	Leonard	KCL Institute of Psychiatry	leonard.schalkwyk@kcl.ac.uk
Stephens	Dai	University of Sussex	d.stephens@sussex.ac.uk
SUN	Xia	CNRS UMR 8195 Universite Paris Sud	xia.sun@u-psud.fr
Sungur	Ayse Oezge	Philipps-University of Marburg	oezge.sungur@staff.uni-marburg.de
Syed	Sheyum	University of Miami	sheyum@physics.miami.edu
Tarantino	Lisa	University of North Carolina	lisat@med.unc.edu
Thompson	Claudia	The College of Wooster	crt@wooster.edu
van Swinderen	Bruno	The University of Queensland	b.vanswinderen@uq.edu.au
Verstreken	Patrik	KU Leuven	ingrid.pintens@med.kuleuven.be
Waddell	Scott	Oxford Martin School University of Oxford	scott.waddell@cncb.ox.ac.uk
Welberg	Leonie	Nature Publishing Group	l.welberg@nature.com
Williams	Robert	University of Tennessee Health Science Center	rwilliams@uthsc.edu
Winters	Boyer	University of Guelph	bwinters@uoguelph.ca
Yaksi	Emre	KULeuven	emre.yaksi@nerf.be