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International Behavioural and Neural Genetics Society

17th Annual Genes, Brain & Behaviour Meeting

Evolutionary Biology Centre

Uppsala University, Sweden

May 19 – 22, 2015

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International Behavioural and Neural Genetics Society

Genes, Brain, and Behavior 2015

17th Annual Meeting of the International Behavioural and Neural Genetics Society

May 19 – 22, 2015

Uppsala, Sweden

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Save the Date!

Genes, Brain and Behavior 2016

Bar Harbor, Maine, USA.
May 13-17, 2016
Local Host: Elissa Chesler

Organizers

Local Hosts and Organizing Committee

Lina Emilsson
Petronella Kettunen
Elena Jazin

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Steve Boehm
Lisa Tarantino
Marissa Ehringer
Chen Gang
Karl Clark
Chris Kliethermes
Elissa Chesler

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Jacqueline Crawley (2012-2014)
Stephen Boehm (2012-2014)
Maria Luisa Scattoni (2013-2015)
Josh Dubnau (2014-2015)
Marissa Ehringer (2014-2016)
Robert Gerlai (2014-2016)

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Travel Awardees 2015

Applicant's Name	Affiliation	Country
Graduate Students		
Calleja-Conde Javier	Complutense University of Madrid	Spain
Caruso Angela	Istituto Superiore di Sanità	Italy
Cousin Margot	Mayo Clinic, Rochester	USA
Echeverry-Alzate Víctor	Complutense University of Madrid	Spain
Fursenko Dariya	Institute of Cytology and Genetics, Novosibirsk	Russia
Hobbs Eleanor *	MRC Harwell, Oxford Univ	UK
Hovey Daniel	Gothenburg University	Sweden
Ilchibaeva Tatiana	Institute of Cytology and Genetics, Novosibirsk	Russia
Krug Randall	Mayo Clinic, Rochester	USA
Kulikova Elizabeth	Institute of Cytology and Genetics, Novosibirsk	Russia
Majdak Petra	Univ of Illinois at Urbana-Champaign	USA
Poggini Silvia	Istituto Superiore di Sanità	Italy
Schoenrock Sarah	Univ of North Carolina, Chapel Hill	USA
Shorter John	North Carolina State Univ	USA
Silva-Silva Daniel	Federal Univ of Minas Gerais	Brazil
Strenn Nina	University of Gothenburg	Sweden
Tunc-Ozcan Elif	Northwestern Univ	USA
van Dijk Maarten	Univ of Zurich	Switzerland
Wade Mark	Univ of Toronto	Canada
Yang Joanna	Mayo Clinic, Rochester	USA
Yazdani Neema *	Boston Univ	USA
Postdocs		
Balcells Ingrid	Univ of Helsinki	Finland
Giardino William *	Stanford Univ	USA
Hamilton Gillian	Univ of Illinois at Urbana-Champaign	USA
Liang Zhengzheng Sophia	Wellcome Trust Sanger Institute	UK
Matthews Ben	Rockefeller University	USA
Saul Michael	Univ of Illinois at Urbana-Champaign	USA
Scaplen Kristin	Brown Univ	USA
Sittig Laura	Univ of Chicago	USA
Tsybko Anton	Institute of Cytology and Genetics, Novosibirsk	Russia
Junior Faculty		
Chen Gang	Nanjing University of Chinese Medicine	China
Clark Karl	Mayo Clinic, Rochester	USA
Coutellier Laurence	Ohio State Univ	USA
Kamens Helen	Penn State Univ	USA
O'Leary Olivia *	University College Cork, Ireland	UK
Ozburn Angela	Oregon Health & Science Univ	USA
Parker Clarissa	Middlebury College	USA

*** Outstanding Awardees**

Program overview

	Tuesday, 19/5/15	Wednesday, 20/5/15	Thursday, 21/5/15	Friday, 22/5/15
08:00		Registration and morning coffee	Registration and morning coffee	Registration and morning coffee
08:30		**Keynote Lecture** Ekmansalen Per Jensen *Title: Genetics and epigenetics of domesticated social behavior.*	**Presidential Lecture** Ekmansalen Patrick Sullivan, MD *Title: Where we are and where we need to be in psychiatric genomics.*	**Young Investigator Lecture**, Ekmansalen Yehuda Ben-Shahar, PhD *Title: The genetics of neuronal and behavioral homeostasis.*
09:00				
09:30		**Coffee Break 30 min**	**Coffee Break 30 min**	**Coffee Break 30 min**
10:00		**Symposium III** Ekmansalen *Title: Neurogenomics of social behaviour* Chair: Svante Winberg & Rui F. Oliveira	**Symposium V** Ekmansalen *Title: The Role of Impulsivity in Addiction* Chair: Lisa M. Tarantino	**Symposium VII** Ekmansalen *Title: Circuit and Molecular Mechanisms in Disordered Eating Animal Models* Chair: Andrew Hardaway
10:30				
11:00	**Registration** At EBC, Norbyvägen 14			
11:30				
12:00	**Symposium I** Ekmansalen *Title: Genetic and epigenetic regulation of stress-related behaviors* Chair: Gang Chen & Abraham Palmer	**Lunch 1h** Mickes kök	**Lunch 1h**, Mickes kök Zeiss lunch presentation	**Lunch 1h** Mickes kök
12:30				
13:00		**Outstanding Travel Award Talks** Ekmansalen Chair: Mark Rutledge-Gorman	**Symposium VI** Ekmansalen *Title: Vesicular glutamate transporters: from synaptic physiology to pathophysiology* Chair: Åsa Wallén-Mackenzie & Salah El Mestikawy	**Selected Talk Session II** Ekmansalen
13:30				
14:00				
14:30	**Coffee Break 30 min**	**Coffee Break 30 min**		
15:00	**Symposium II** Ekmansalen *Title: Epigenomic mechanisms of neuroadaptation and neurodegeneration* Chair: Alfredo Ghezzi	**Symposium IV** Ekmansalen *Title: Oxytocin and social behaviours: From fish to human* Chair: Petronella Kettunen & Lars Westberg	**Coffee Break 30 min**	**Coffee Break 30 min**
15:30			**Selected Talk Session I** Ekmansalen Chair: Elena Jazin	**Symposium VIII** Ekmansalen *Title: Next3: Next generation neuroscience questions, Next generation speakers, next generation sequencing.* Chair: Josh Dubnau
16:00				
16:30				
17:00	**Opening Reception**	**Coffee Break 30 min**	**General Business Meeting**, Ekmansalen	
17:30		**Distinguished Scientist Award Lecture** Ekmansalen	**Poster Session and Pub** Mickes kök	**Banquet** Mickes kök Three course dinner Pub and Dancing
18:00				
18:30		**Conclusion of Day 2**		
19:00	**Conclusion of Day 1**		**Conclusion of Day 3**	
19:30				
20:00				

Meeting program in detail

Tuesday, May 19

11:00 REGISTRATION

12:00 WELCOME TO IBANGS 2015
Lisa Tarantino & Lina Sors Emilsson

12:30 SYMPOSIUM I

Genetic and epigenetic regulation of stress related behaviors.
Chairs: Gang Chen, Nanjing University of Chinese Medicine, China, and Abraham Palmer, University of Chicago, USA

12:30 Chadi Touma, Max Planck Institute of Psychiatry, Germany.
Mice selected for extremes in stress reactivity reveal key endophenotypes of major depression: A translational approach.

13:00 Olivia O'Leary, University College Cork, Cork, Ireland.
GABAB(1) receptor subunit isoforms differentially regulate stress resilience.

13:30 Han Wang, Soochow University, China.
A circadian model for Attention-Deficit Hyperactivity Disorder (ADHD).

14:00 Gang Chen, Nanjing University of Chinese Medicine, China.
Strain dependent enduring antidepressant effects of Yueju and ketamine are associated with CREB signaling in the hippocampus of the mouse brain.

14:30 COFFEE BREAK

15:00 SYMPOSIUM II

Epigenomic mechanisms of neuroadaptation and neurodegeneration.
Chairs: Alfredo Ghezzi, University of Texas at Austin, USA, and Matthew Reilly, Division of Neuroscience & Behavior, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, USA

15:00 Georgy Bakalkin, Uppsala University, Uppsala, Sweden.
A role of the epigenome in alcoholism: Genetically-regulated trajectories of DNA methylation in human brain.

15:30 Nigel S. Atkinson, University of Texas at Austin, USA.
Using histone marks to identify behaviorally relevant alcohol response genes.

16:00 Susan Bergeson, Texas Tech University Health Sciences Center, USA.
Bioinformatics analyses of alcohol-mediated molecular and epigenetic changes reveal age-specific differences in brain and pharmacotherapeutic treatment potential.

16:30 Leonard Schalkwyk, University of Essex, UK.
DNA methylation profiles in Alzheimer disease brains.

17:00 OPENING RECEPTION

Enjoy a glass of wine and light hors d'oeuvres while networking with colleagues. Followed by a leisurely walk through Uppsala's historical areas accompanied by a local guide. The tour will end near the hotels. Please inform IBANGS Central Office (administrator@ibangs.org) if you are unable to participate in the hour walk and need alternative guided transportation. Please be prepared for sun or rain. May temperatures average 41-61°F (5-16°C).

Wednesday, May 20

8:00 REGISTRATION AND COFFEE

8:30 KEYNOTE LECTURE

Per Jensen, Linköping universitet, Sweden.
Genetics and epigenetics of domesticated social behavior.

9:30 COFFEE BREAK

10:00 SYMPOSIUM III

Neurogenomics of social behavior.
Chair: Svante Winberg, Uppsala University, Sweden, and Rui F. Oliveira University of Lisbon, Portugal

10:00 Svante Winberg, Uppsala University, Sweden.
Stress coping styles in teleost fish – genetic factors and plastic responses to social experience.

10:30 Elena Jazin, Uppsala University, Sweden.
Cellular sexual dimorphism of X and Y homologous gene expression in human central nervous system during early male development.

11:00 Galit Shohat-Ophir, Bar-Ilan University, Israel.
Social experience modulates group interaction in Drosophila melanogaster.

11:30 Rui F. Oliveira University of Lisbon, Portugal.
Neuromolecular mechanisms of social learning in zebrafish.

12:00 LUNCH

13:00 OUTSTANDING TRAVEL AWARD TALKS

Chair: Mark Rutledge-Gorman, Oregon Health & Science University and Portland VA Medical Center, USA

13:10 Neema Yazdani, Boston University School of Medicine, USA.
Hnrnph1 is a quantitative trait gene for methamphetamine sensitivity.

13:30 William J. Giardino, Stanford University, USA.
Genetic dissection of extended amygdala circuitry linking anxiety, aversion, and behavioral arousal.

13:50 Eleanor Hobbs, MRC Harwell, UK.
Validation of the candidate risk gene for neuropsychiatric disease CACNA1C using a mouse ENU mutagenesis screen.

** Olivia O'Leary, University College Cork, Cork, Ireland.
GABAB(1) receptor subunit isoforms differentially regulate stress resilience.
**Honored as Outstanding Travel Awardee; presented talk in Symposium I.

14:10 Antonio Noronha, Director, Division of Neuroscience & Behavior, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, USA.
NIAAA research and training priorities.

14:30 COFFEE BREAK

15:00 SYMPOSIUM IV

Oxytocin and social behaviours: From fish to human.
Chair: Petronella Kettunen,University of Gothenburg, Sweden, and Lars Westberg, University of Gothenburg, Sweden

15:00 Petronella Kettunen, University of Gothenburg, Sweden.
Using zebrafish to study the role of oxytocin in social behavior.

15:30 Sietse F. de Boer, University of Groningen, The Netherlands.
The promise and perils of oxytocin as neurochemical mediator of sociality: insights from rodent studies.

16:00 Lars Westberg, University of Gothenburg, Sweden.
Variants of the oxytocin receptor gene and human social behaviors.

16:30 Siri Leknes, Oslo University Hospital, Norway.
Oxytocin treatment in humans –reliable and variable effects.

17:00 COFFEE BREAK

17:30 DISTINGUISHED SCIENTIST AWARD LECTURE

Dai Stephens, University of Sussex Brighton, United Kingdom.

Thursday, May 21

8:00 REGISTRATION AND COFFEE

8:30 PRESIDENTIAL LECTURE

Patrick Sullivan, University of North Carolina, USA.
Where we are and where we need to be in psychiatric genomics.

9:30 COFFEE BREAK

10:00 SYMPOSIUM V

The role of impulsivity in addiction.

Chair: Lisa M. Tarantino, University of North Carolina at Chapel Hill, USA.

10:00 Erika Roman, Uppsala University, Uppsala, Sweden.
Risk-related behaviors and propensity for excessive alcohol intake.

10:30 Nicholas Grahame, Indiana University, Purdue University, USA.
High Impulsivity, poor response inhibition, and prevalent habitual behavior associate with genetic differences in volitional alcohol intake.

11:00 Chiara Giuliano, University of Cambridge, UK.
Compulsive alcohol-seeking behavior is attenuated by inhibiting μ-opioid receptors.

11:30 J. David Jentsch, University of California, Los Angeles, USA.
Genetic analyses of impulsivity and motivated behavior as addiction-relevant traits.

12:00 LUNCH

12.30 Lunch Seminarium: Zeiss

Lightsheet Z.1: Advances in tissue clearing. Fast and deep tissue imaging

13:00 SYMPOSIUM VI

Vesicular glutamate transporters: from synaptic physiology to pathophysiology.

Chairs: Åsa Wallén-Mackenzie, Uppsala University, Sweden and Salah El Mestikawy, McGill University, Canada and Université Pierre et Marie Curie, France.

13:00 Christian Rosenmund, Charité - Universitätsmedizin Berlin, Germany.
Glutamate-GABA cotransmission in cultured forebrain neurons.

13:30 Louis-Eric Trudeau, Université de Montréal, Canada.
Role and topography of glutamate release sites in dopamine neurons.

14:00 Stefano Pupe, Uppsala University, Sweden.
New subpopulations within the brain reward system.

14:30 Salah El Mestikawy & Stephane Jamain (shared talk), McGill University, Montreal, Canada; Université Pierre et Marie Curie, France.
VGLUT3: From glutamate synapses to pathophysiology of psychiatric disorders.

15:00 COFFEE BREAK

15:30 SELECTED TALKS I

Chair: Elena Jazin, Uppsala University, Sweden

15:40 Patrick Martin Nolan, Harwell Science and Innovation Campus, Oxfordshire, UK.
Loss of function of the microtubule severing enzyme KATNAL1 underlies defects in behaviour, neuronal migration and neuronal morphology.

16:00 Sihhui Huang, University of Zurich, Switzerland.
Domestication by selecting for tameness increases adult hippocampus neurogenesis in middle and temporal hippocampus in foxes.

16:20 Silvia Poggini, Istituto Superiore di Sanità, Italy.
The double outcome of antidepressant treatment depends on the quality of the living environment.

16:40 Laurence Coutellier, The Ohio State University, USA.
Abnormal juvenile maturation of the GABAergic system in the prefrontal cortex of Npas4 deficient mice.

17:00 GENERAL BUSINESS MEETING

17:30 POSTER SESSION AND PUB

1. Magdalena Janecka, King's College London, United Kingdom. *Effects of advanced paternal age on trajectories of social behavior and motor development in offspring.*
2. Stina Lundberg, Uppsala University, Sweden. *Prolonged maternal separation affect corticosterone levels and social play behavior in adolescent male but not female Wistar rats.*
3. Mia Persson, Linköping University/IFM, Sweden. *Heritability of human-directed social behaviour in beagles.*
4. Dariya Fursenko, Institute of Cytology and Genetics SB RAS, Russian Federation. *The effect of tumor necrosis factor alpha deficiency on behavior and serotonergic system in mice.*
5. Hanne Løvlie, Linköping University/IFM, Sweden. *The relationship between cognition and personality is task- and age-dependent in the red junglefowl.*
6. Ingrid Balcells, University Helsinki, Finland. *Gene-environment interaction of gene expression in a mouse model of anxiety.*
7. Natalia Bondar, Institute of Cytology and Genetics SB RAS, Russian Federation. *Molecular adaptation to social defeat stress: Effects on prefrontal cortex transcriptome.*
8. Ann-Sofie Sundman, Linköping University/IFM, Sweden. *Behavioural differences and the heritability of behaviour in two selection lines of golden and Labrador retriever.*
9. Vladimir Naumenko, Institute of Cytology and Genetics SB RAS, Russian Federation. *Effect of glial cell line-derived neurotrophic factor on depressive-like behavior, spatial learning and key genes of the brain dopamine system in genetically predisposed to behavioral disorders mouse strains.*
10. Elena Kondaurova, Institute of Cytology and Genetics SB RAS, Russian Federation. *Effect of chronic activation of 5-HT7 receptors on behavior, 5-HT7 and 5-HT1A receptors functional activity, and expression of key genes of the brain serotonin system.*
11. Gillian Hamilton, University of Illinois Urbana-Champaign, United States. *Voluntary exercise rescues behavioral deficits induced by neonatal alcohol exposure and increases adult hippocampal neurogenesis in mice.*
12. Glenda Lassi, Istituto Italiano di Tecnologia, Italy. *Dissecting Parent-of-origin Effects in Attachment, Anxiety, Social Behaviour and Vocalizations: a Longitudinal Investigation in Mice.*
13. Emily Moore, North Carolina State University, United States. *Species-specific behavioral types are associated with microhabitat differentiation in Malawi African cichlid fishes.*
14. Benjamin Matthews, The Rockefeller University, United States. *Genome engineering and oviposition behavior in the mosquito Aedes aegypti.*
15. Petra Majdak, UIUC, United States. *Selective breeding for home cage hyperactivity produces hyperactive-impulsive behavioral deficits which are ameliorated by therapeutic amphetamine.*
16. Charlotte Rosher, Linköping University/IFM, Sweden. *Like father, like son: Do old male fowl show less aggression towards son's mating opportunities?*
17. Silke Dietze, FU-Berlin, Germany. *8-OH-DPAT and thermoregulation in 5-HT1A-receptor mutant mice.*
18. Mark Wade, University of Toronto, Canada. *Oxytocin and vasopressin genes in children's externalizing psychopathology: a cognitive endophenotype approach.*
19. John Shorter, North Carolina State University, United States. *Epistasis and the Genetic Architecture of Drosophila Aggressive Behavior.*
20. Johan Bélteky, Linköping University/IFM, Sweden. *The search for stress-sensitive time early periods in the precocial chicken.*
21. Sara Ekmark Lewén, Uppsala University Sweden. *Behavioral Facility (UUBF) – for the study of mouse, rat and fish behavior.*

22. Michael Saul, University of Illinois, United States. *Born to run: The neural transcriptome signature of mice selectively bred for high voluntary wheel running*.
23. Roelof Maarten van Dijk, University of Zurich, Switzerland. *Adult neurogenesis modulates novelty exploration.*
24. Kristin Scaplen, Brown University, United States. *Dopamine Bi-directionally Regulates Alcohol Memory Valence.*
25. Elif Tunc-Ozcan, Northwestern University, United States. *Intergenerational consequences of fetal programing by in utero exposure to ethanol in rats.*
26. Laura Sittig, University of Chicago, United States. *Genome-wide association for prepulse inhibition in mice implicates hippocampal expression QTL for Ambra1.*
27. Angela Caruso, Istituto Superiore di Sanità, Italy. *The role of chromatin remodelling factor CHD7 in cerebellar development and autism in a conditional mouse line.*
28. Nadine Schweizer, Uppsala University, Sweden. *A Vglut2/Pitx2 subpopulation of the subthalamic nucleus is important for regulation of locomotion and reward processing.*
29. Martin Johnsson, Linköping University/IFM, Sweden. *Genetical genomics of fearful behaviours under chicken domestication.*
30. Angela Ozburn, Oregon Health & Science University, United States. *Effects of Pharmacogenetic Manipulation of the Nucleus Accumbens on Neuronal Activity and Alcohol-Related Behaviors.*
31. Darya Bazovkina, Institute of Cytology and Genetics SB RAS, Russian Federation. *Involvement of C1473G polymorphism in mouse Tph2 gene in chronic ethanol treatment effect on behavior, 5-HT1A, BDNF and TrkB genes expression in brain.*
32. Eric Klee, Mayo Clinic, United States. *Drug Repurposing for Tobacco Dependence Treatment.*
33. Stephen Boehm, Indiana University - Purdue University Indianapolis, United States. *Development of a mouse model of adolescent binge caffeinated alcohol consumption.*
34. Emelie Jansson, Linköping University/IFM, Sweden. *Is optimism affected by personality? A test of cognitive judgment bias in red junglefowl chicks.*
35. John Crabbe, VA Portland Health Care System, United States. *Dual-trait Selection for Excessive Alcohol Drinking.*
36. Anton Tsybko, Institute of Cytology and Genetics SB RAS, Russian Federation. *Effect of microgravity on GDNF and CDNF genes expression in the mouse brain.*
37. Tatiana Ilchibaeva, Institute of Cytology and Genetics SB RAS, Russian Federation. *Alteration of BDNF expression in genetically defined highly aggressive and nonaggressive rats.*
38. Elizabeth Kulikova, Institute of Cytology and Genetics SB RAS, Russian Federation. *The effects of TC-2153 on behavior, serotonin system and BDNF in mice with different predisposition to catalepsy.*
39. Thomas Viereckel, Uppsala University, Sweden. *Gene expression diversity in the ventral tegmental area, substantia nigra and subthalamic nucleus .*
40. Daniel Hovey, Gothenburg University, Sweden. *Antisocial behavior and genetic variation in the oxytocin receptor.*
41. Magda Teles, Instituto Gulbenkian de Ciência, Portugal. *Socially driven changes in neural and behavioural plasticity in zebrafish.*
42. Hans-Peter Lipp, University of Zurich, Switzerland. *Laboratory mouse lines derived from outdoor natural selection tested in IntelliCages: reduced initial novel object exploration and prolonged place avoidance.*
43. Igor Ponomarev, University of Texas at Austin, United States. *Defining global histone 3 lysine 4 trimethylation changes in human alcoholism using ChIP-Seq.*
44. Jose Antonio Lopez-Moreno, Complutense University of Madrid, Spain. *Behavioral and epigenetic characterization of alcohol and energy drink interactions.*
45. Victor Echeverry Alzate, Complutense University of Madrid, Spain. *A translational study of alcohol binge in rats and humans: gene expression profiling of histone deacetylases in blood.*
46. Xavier Cousin, Ifremer, France. *Embryo-larval stress exposure modifies behaviour ontogeny and genes expression in zebrafish.*
47. Inga Poletaeva, Moscow State University, Russian Federation. *Brain weight and behavioral differences in mouse strains selected for different brain weigh after the selection stopped.*

48. Bryn Farnsworth, Uppsala University, Sweden. *Zebrafish quaking genes are associated with nervous system development*
49. Joanna Yang, Mayo Clinic, United States. *An InSciEd Out Intervention in Adolescent Mental Health.*
50. Javier Calleja, Complutense University of Madrid, Spain. *Effects of Nalmefene on alcohol and co-administration of cocaine.*
51. Alfredo Ghezzi, University of Texas at Austin, United States. *Epigenetic modulation of long-term neuroadaptation to alcohol by the histone acetyl-transferase CBP.*
52. Helen Kamens, Penn State University, United States. *The Influence of ADOLESCENT Nicotine exposure on Alcohol Consumption and gene expression.*
53. Sabine Cordes, Lunenfeld-Tanenbaum Research Institute, Canada. *Essential roles for the splicing regulator nSR100/SRRM4 during nervous system development.*
54. Alexandros Lordos, University of Cyprus, Cyprus. *The neurobiological basis of antisocial behavior: Insights from a molecular genetic family based association study.*
55. Georgia Zacharaki, University Of Cyprus, Cyprus. *Do Autism and Callous Unemotional Traits (CU Traits) possess a shared molecular genetic background?*
56. Randall Krug, Mayo Clinic, United States. *Elucidating Cannabinoid Biology in Zebrafish.*
57. Bryant Camron, Boston University School of Medicine, United States. *QTL mapping of binge eating to the Cyfip2 locus in C57BL/6 substrains: Implications for hyperphagia in Prader-Willi Syndrome.*
58. Josefina Zidar, Linköping University/IFM, Sweden. *Early environmental enrichment generates stress resilience and more optimistic chicks.*
59. Clarissa Parker, Middlebury College, United States. *Measuring conditioned fear in Diversity Outbred mice.*
60. Nina Strenn, University of Gothenburg, Sweden. *Associations between genetic variations in IL1B and brain region volumes in bipolar patients and controls.*
61. Sarah Schoenrock, University of North Carolina at Chapel Hill, United States. *Effects of maternal diet during the perinatal period on gene expression and behavior in mice.*
62. Karl Clark, Mayo Clinic, United States. *Developing zebrafish methodology to model genetic and environmental modifiers of the vertebrate stress response system (SRS).*
63. Margot Cousin, Mayo Clinic, United States. *Individualizing the Treatment of Tobacco Dependence by Assessing Behavioral Endophenotypes and Molecular Adaptations in Zebrafish.*
64. Daniel Silva e Silva, Federal University of Minas Gerais, Brazil. *Alcoholism - Identification of molecular targets by analysis of transcript levels of NA alcohol addiction model.*
65. Elena Jazin, Uppsala University, Sweden. *Cellular sexual dimorphism of X and Y homologous gene expression in human central nervous system during early male development.*
66. Martin Johansson, Uppsala University, Sweden. *SNP array analysis of copy number variants on the human Y chromosome reveals novel and frequent duplications overrepresented in specific haplogroups.*

Friday, May 22

8:00 REGISTRATION AND COFFEE

8:30 YOUNG INVESTIGATOR LECTURE

Yehuda Ben-Shahar, Washington University, USA.
The genetics of neuronal and behavioral homeostasis.

9:30 COFFEE BREAK

10:00 SYMPOSIUM VII

Circuit and Molecular Mechanisms in Disordered Eating Animal Models.
Chair: Andrew Hardaway, University of North Carolina at Chapel Hill, USA.

10:00 Pietro Cottone, Boston University, USA.
High trait impulsivity predicts food addiction-like behavior in the rat.

10:30 Ida Nilsson, Karolinska Institutet. Sweden.
The anorexia of the anx/anx mouse is associated with hypothalamic degeneration and mitochondrial dysfunction.

11:00 Andrew Hardaway, University of North Carolina at Chapel Hill, USA.
Nociceptin signaling modulates the expression of limited access binge eating.

11:30 Lora Heisler, University of Aberdeen, UK.
Subset of POMC peptides controlling ingestive behavior and body weight.

12:00 LUNCH

13:00 SELECTED TALK SESSION II

Chair: Lina Emilsson and Elena Jazin, Uppsala University, Sweden

13:00 Palle Dunn Rohde, Aarhus University, Denmark.
Functional insight from fruit flies on human ADHD candidate genes.

13:20 Zhengzheng Sophia Liang, Wellcome Trust Genome Campus, UK.
Transcriptomic analysis of allelic imbalance in the mouse olfactory system.

13:40 Michael Parsons, Harwell Science and Innovation Campus, UK.
Short-circuit: Characterization of a transcription factor that activates a novel circadian transcriptional axis.

14:00 Daniel Nätt, Linkoping University, Sweden.
Stress in five-year-old children cause whole-genome loss of DNA-methylation in endogenous retroviruses - the link to adult neuropsychiatric disorder.

14:20 Hee-Sup Shin, Institute for Basic Science (IBS), Korea.
Preventing return of fear by extinction training coupled with alternating bilateral stimulation increases BDNF and inhibitory transmission in amygdala: A neural mechanism of the psychotherapy for posttraumatic stress disorder.

14:40 Cynthia Bulik, University of North Carolina at Chapel Hill, USA.
The gut-brain axis in acute anorexia nervosa: Associations between intestinal microbiota and psychopathology measures.

15:00 COFFEE BREAK

15:30 SYMPOSIUM VIII

Next3: Next generation neuroscience questions, Next generation speakers, Next generation sequencing.

Chair: Joshua Dubnau, Cold Spring Harbor Laboratory, USA

15:30 Lee Henry, The Janelia Research Campus of the Howard Hughes Medical Institute. USA.
Application of the INTACT system to the study of neuronal cell types.

16:00 Amanda Crocker, Princeton University, USA.
Transcriptome - Wide Analysis of Single Drosophila Mushroom Body Neurons Reveals Learning Related Changes in Gene Expression.

16:30 Benjamin J. Matthews, Rockefeller University, USA.
Genome engineering and oviposition behavior in the mosquito Aedes aegypti.

17:00 Mike Lodato, Harvard University, USA.
Mosaic single nucleotide mutations record developmental and mutational histories of single neurons in human cerebral cortex.

17:30 BANQUET

Conference Information

Conference venue

The conference will be held at the Evolutionary Biology Center (EBC) at Uppsala University. The venue is in on the ground floor in the core lecture building, Norbyvägen 14, in the lecture hall called "Ekmansalen". See link for maps **http://ebc.uu.se/Find+EBC/**

To reach EBC it possible to walk or go by bus number 6 or 7 from the center where the hotels are located. The walk is about 10 blocks (15 min) through the historic parts of Uppsala including passing by Uppsala Castle, the university library "Carolina Rediviva" and the botanical garden, constructed by Carl Von Linnaeus in the 18th century.

Internet connection

A personal internet connection will be available to all registered attendees. If you're an employee/Ph.D. or student at a university you can also connect to Eduroam. In order to do this you need to connect the same way as you do on your own campus. If you are not sure on how to do this, contact the IT-department at your own university before departure to the meeting.

Coffee, Lunch and Social activities during the meeting

Coffee

Coffee, tea and water will be served in the breaks during the conference. In the morning breaks will sandwiches be served and in the afternoon break cakes.

Lunch

Lunch will be served Wednesday (20/5) to Friday (22/5) at "Mickes kök" a restaurant located above the conference venue at EBC. As warm lunch will be served everyday, we kindly ask everyone to go as quickly as possible to the restaurant after the session before lunch has ended. Thanks!

Opening reception

Enjoy a glass of wine and light hors d'oeuvres while networking with colleagues. Followed by a leisurely walk through Uppsala's historical areas accompanied by a local guide. The tour will end near the hotels. Please inform IBANGS Central Office (administrator@ibangs.org) if you are unable to participate in the hour walk and need alternative guided transportation. Please be prepared for sun or rain. May temperatures average 41-61°F (5-16°C).

Poster session

Poster session will take place Thursday, May 21, between 5.30 pm and 7.30 pm.

During the poster session, snacks will be served and there will be a cash bar.

Closing banquet

The closing banquet will be staged in the restaurant area above the conference venue at EBC. A three-course dinner will be served. After the dinner, there will be a cash bar, music and dancing.

How to get to Uppsala from Arlanda airport

By bus

Bus 801 runs between Stockholm-Arlanda International Airport and Uppsala city. The bus runs 2-3 times every hour from 6 a.m. to midnight. The trip takes about 35 minutes. The price is SEK 90 and you buy the ticket from the driver. Only Swedish currency or major credit cards are accepted at the bus.
More information: **http://www.ul.se**

By train

Trains leave Stockholm-Arlanda for Uppsala Central station directly from Sky City. You can buy tickets at the airport railway station. The price is about SEK 87 - 135. You can search for departures at **http://www.sj.se/** or **www.uls.se** (Upptåget). The trip takes 15-20 minutes.

By taxi

There are also several taxi companies operating from the airport. The ride takes about 30 minutes and costs approx. SEK 435. If you intend to take a taxi, we recommend you to agree a fare in advance. The international phone number to the largest taxi company in Uppsala is +46 18 100 000 (Uppsala Taxi).

Information on sightseeing opportunities

In Uppsala almost all hotels, restaurants, cultural attractions and places of entertainment are within walking distance. There is an extensive network of local busses for travel within Uppsala. Below are six of the top historic sightseeing attractions.

Uppsala Cathedral (Uppsala domkyrka)

Scandinavia's biggest and tallest church. As long as it is tall, at 118.7 m, the church is the seat of the archbishop and was built between 1270 and 1435. It contains the shrine of Eric IX of Sweden (Eric the Holy) and a Baroque pulpit. The graves of Kings Gustavus Vasa and Johan III, Linnaeus, Olof Rudbeck, Nathan Söderblom and others are here.

Uppsala Castle (Uppsala slott)

The castle was built in the 1540s, and has a dramatic history. Many key events in Swedish history have been played out here. Fredens Hus (House of Peace) is here, with an exhibition about the former UN Secretary General Dag Hammarskjöld and his achievements.

Old Uppsala (Gamla Uppsala)

Old Uppsala is one of Scandinavia's most important historic areas, with three royal burial sites dating from the 6th century. Gamla Uppsala museum offers a fascinating journey through time. From 6th century pagan kingdoms to the introduction of Christianity. This marked the end of the Viking Age, and the start of construction of the old cathedral in the 12th century.

Museum Gustavianum

Sweden's oldest university building is home to collections representing both the university and the history of science. The Anatomical Theatre was used for public dissections between the mid-17th and mid-18th centuries. The archaeological exhibition displays the Vikings and their ancestors. The museum's collections also include treasures from antiquity and the Augsburg Art Cabinet.

Linnaeus Museum & Linnaeus Garden (Linnémuseet och Linnéträdgården)

The Professor's Residence, once the home of Linnaeus (1707-1778), is now a museum displaying the famous botanist's great scientific achievements. The building dates from the 18th century, and holds original furniture, clothing, fabrics and china. The Linnaeus Garden was laid out in about 1655. Today, about 1300 plants are grown there, and the beds are arranged according to Linnaeus' sexual system.

Carolina Rediviva

University library and the oldest library in Sweden. Today, the collections hold more than five million books. The exhibition hall displays include the 6th-century Silver Bible which is now on UNESCO's Memory of the World Register, and some of Mozart's original scores.

Uppsala is also close to Stockholm (70 km) and there are both busses (1h) and trains (40 min) connecting the two cities.

Destination Uppsala

For more information about Uppsala and restaurants please visit link to Destination Uppsala.
http://www.destinationuppsala.se/en/

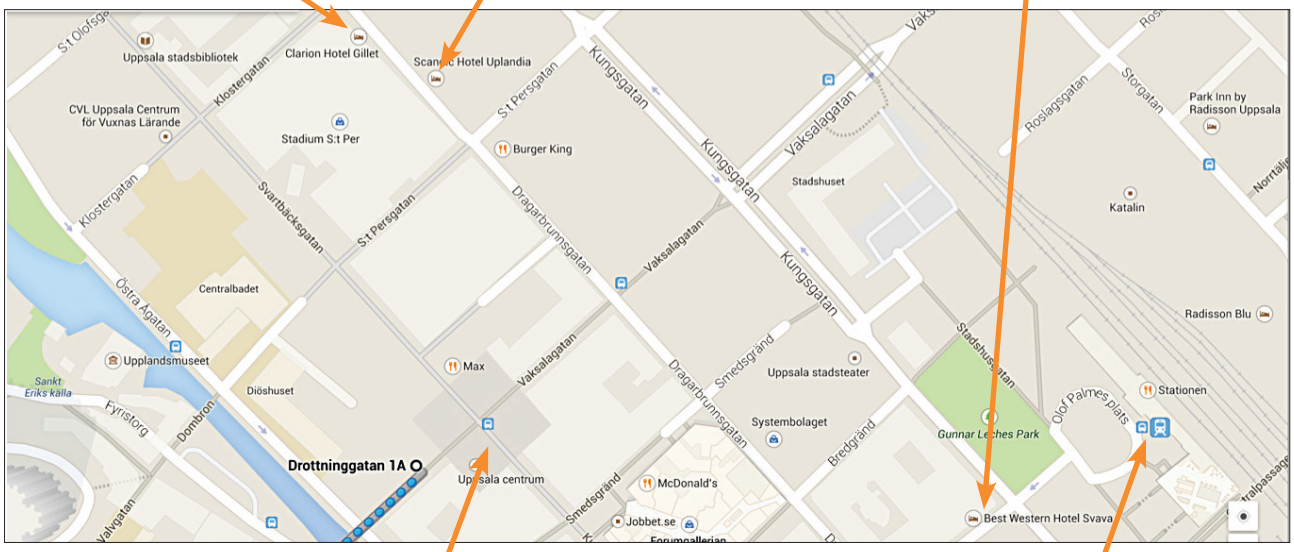
Maps

Locations of Hotels and Uppsala Central station

Clarion Hotel Gillet
Dragarbrunnsgatan 23

Scandic Uplandia
Dragarbrunnsgatan 32

Best Western Hotel
Bangardsgatan 24



City center - Drottninggatan
"stora torget" where bus 6 & 7
depart towards the Venue at EBC

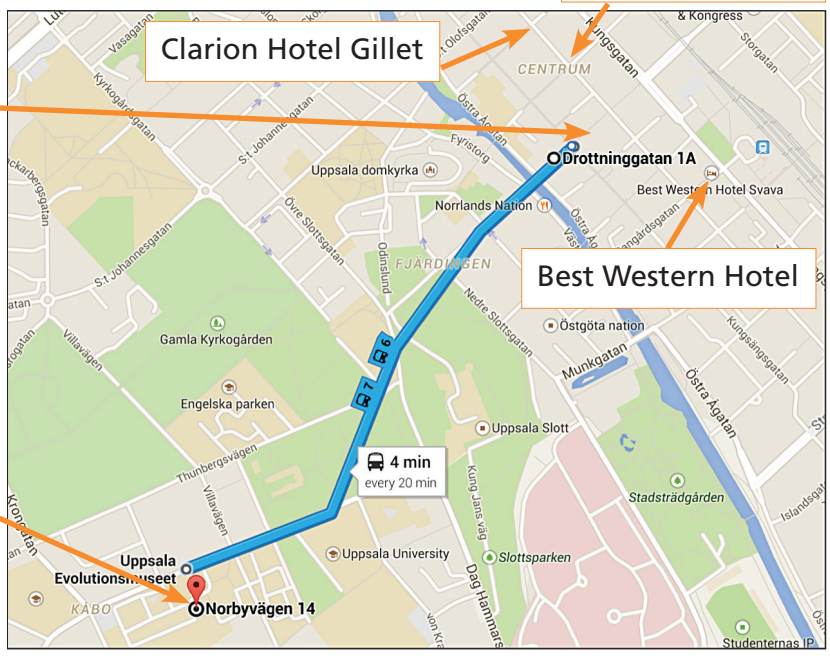
Uppsala Central station
Kungsgatan

Bus direction to the conference venue

Scandic Uplandia

City center "stora torget"
where bus 6 & 7 depart
towards EBC
Bus ride takes around 4 min
and end station is
"The museum of Evolution"

Clarion Hotel Gillet



Best Western Hotel

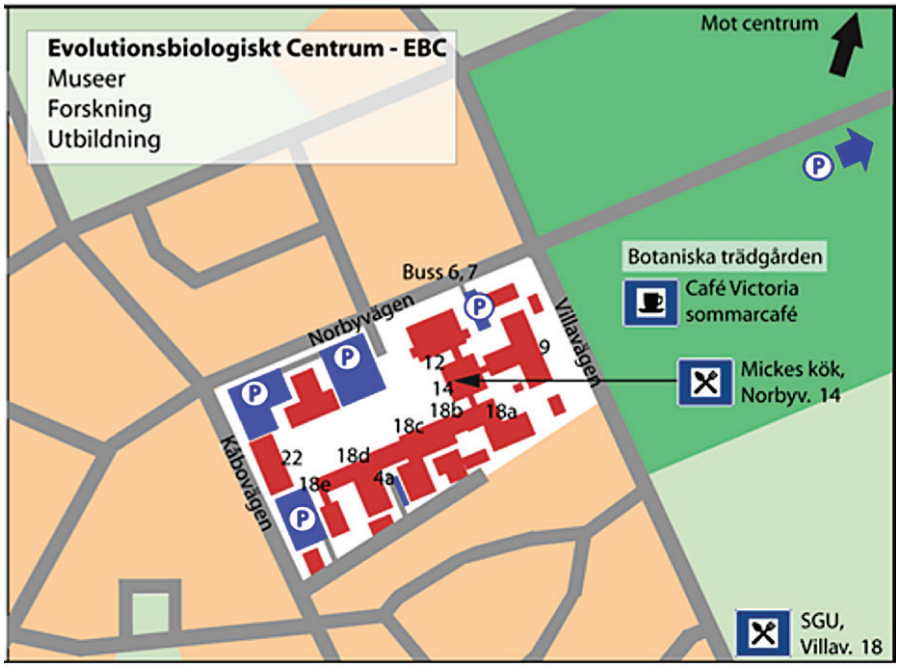
Conference Venue
Norbyvägen 14

Bus 6 & 7 stops at the station
named
"The museum of Evolution"

Walking direction to the conference venue

City center "stora torget" where bus 6 & 7 depart towards EBC

Bus ride takes around 4 min and end station is "The museum of Evolution"



Talk Abstracts

Talk: Chadi Touma, Tuesday May 19, 12:30

Mice selected for extremes in stress reactivity reveal key endophenotypes of major depression: a translational approach

JM Heinzmann[1], S Kloiber[1], G Mattos[1], M Bielohuby[2], MV Schmidt[1], R Palme[3], F Holsboer[1], M Uhr[1], M Ising[1], C Touma[1]

Clear evidence has linked dysregulated hypothalamus-pituitary-adrenocortical (HPA) axis function to the aetiology and pathophysiology of major depression (MD), as observed in the majority of patients. Increased stress reactivity and hyperactivity of the HPA axis seem characteristic for psychotic/melancholic depression, while the atypical subtype of depression has been connected with the opposing phenotypes. However, the underlying molecular-genetic mechanisms are poorly understood.

In the present study, mouse lines selectively bred for extremes in stress reactivity (SR), i.e. presenting high (HR) or low (LR) corticosterone secretion in response to stressors, were used to characterise the molecular alterations on all levels of the HPA axis. Results were contrasted with clinical phenotypes of MD patients from the Munich Antidepressant Response Signature project, stratified according to their cortisol response in the Dex/CRH test.

Distinct differences between HR and LR mice were found in the expression of HPA axis-related genes in the adrenals, pituitary and selected brain areas. Moreover, HR animals presented an enhanced adrenal sensitivity, increased stress-induced neuronal activation in the PVN and an overshooting Dex/CRH test response, whereas LR animals showed a blunted response in these paradigms. Interestingly, analogous neuroendocrine, morphometric, psychopathological and behavioural differences were observed between the respective high and low HPA axis responder groups of MD patients.

Our findings suggests that (i) the SR mouse model can serve as a valuable tool to elucidate HPA axis-related mechanisms underlying affective disorders and (ii) a stratification of MD patients according to their HPA axis-related neuroendocrine function should be considered for clinical research and treatment.

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Talk: Olivia O'Leary, Tuesday May 19, 13:00

$GABA_{B(1)}$ receptor subunit isoforms differentially modulate resilience to stress

OF. O'Leary[1,2] , D. Felice[3], S. Galimberti[1], H. M. Savignac[2], J.A. Bravo[2], T. Crowley[1], M. El Yacoubi[4,5], Jean-Marie Vaugeois[6,7], Martin Gassmann[8], Bernhard Bettler[8], Timothy G. Dinan[2,9], and John F. Cryan[1,2]

Stressful life events increase susceptibility to psychiatric disorders such as depression and anxiety disorders. However, many individuals are resilient to such negative effects of stress. Determining the neurobiology underlying this resilience is instrumental for the development of novel and more effective treatments for stress-related psychiatric disorders. $GABA_B$ receptors are emerging therapeutic targets for the treatment of stress-related disorders such as depression. These receptors are predominantly expressed as heterodimers of a $GABA_{B2}$ subunit with either a $GABA_{B1a}$ or a GABAB1b subunit. Here, we show that specific isoforms of $GABA_B$ receptor subunits differentially regulate stress resilience. Specifically, $GABA_{B(1a)}^{-/-}$ mice are more susceptible whereas $GABA_{B(1b)}^{-/-}$ mice are more resilient to stress-induced anhedonia and psychosocial stress-induced social withdrawal, two features of depression. Furthermore, $GABA_{B(1b)}^{-/-}$ mice are resilient to stress-induced decreases in the survival of newly born cells in the adult hippocampus, and hippocampal $GABA_{B(1b)}$ expression was increased in a genetic mouse model of depression. Taken together, $GABA_B$ receptor subunit isoforms may represent novel therapeutic targets for stress-related disorders.

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8 Department of Biomedicine, University of Basel, 4056 Basel, Switzerland;
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Talk: Han Wang, Tuesday May 19, 13:30

A circadian model for Attention-Deficit Hyperactivity Disorder (ADHD)

H Wang[1,2], J Huang[1,2], Z Zhong[1,2], M Wang[1,2], S Zhang[1,2] and G Huang[1,2]

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most prevalent psychiatric disorders in children and adults. While ADHD patients often display circadian abnormalities, the mechanisms underlying circadian regulation of the pathogenesis of ADHD are unclear. Here we found zebrafish mutants for circadian gene *period1b* (*per1b*) display hyperactive-, impulsive-, attention deficit-like behaviors and low levels of dopamine, reminiscent of human ADHD patients. We found that the circadian clock directly regulates the dopamine catabolism genes *dopamine beta hydroxylase* (*dbh*) and *monoamine oxidase* (*mao*), and likely acts through genes important for the development or maintenance of dopaminergic neurons to regulate their number and organization in the ventral diencephalic posterior tuberculum (PT). We then found that *Per1* knockout mice also display ADHD symptoms and reduced levels of dopamine, thereby implicating circadian roles in ADHD are highly conserved. Our studies demonstrate that disruption of a circadian clock gene elicits ADHD-like syndrome. The circadian model for ADHD sheds light on ADHD pathogenesis and opens avenues for exploring novel targets for diagnosis and therapy for this common psychiatric disorder.

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Funding Support: the key grant program of the National Natural Science Foundation of China (NSFC; 31030062), and the National Basic Research Program of China (973 Program; 2012CB947600)

Talk: Gang Chen, Tuesday May 19, 14:00

Strain dependent CREB signaling in the hippocampus is involved in long-lasting antidepressant effects of Yueju and ketamine

W Xue[1,2], W Wang[3], T Gong[1,2], H Zhang[1,2], W Tao[1,2], L Hu[1,2], G Chen[1,2]*

Individual differences in antidepressant responses are pronounced in both human and animals. Genetic, environmental and neurobiological factors contribute to these poorly understood differences. Ketamine and Yueju are antidepressants which relieve symptoms of depression in a rapid and long-lasting manner after a single administration. It has been shown that antidepressant responses are regulated by CREB, a key transcription factor, and related signaling pathways. The present study was undertaken to test the association of antidepressant effects and CREB signaling using two outbred mouse strains, ICR and Kunming (KM), both of which originate from Swiss mice. Antidepressant effects of a single dose of ketamine or Yueju, as measured by the tail suspension test, lasted for 1 and 5 days in ICR and KM mice, respectively. Up-regulation of total and phosphorylated CREB was detected in KM but not ICR mice at 1 day post-administration of ketamine or Yueju. Consistently, expression of the CREB signaling activator, PKA and the CREB effector, BDNF, were up-regulated in KM but not ICR mice. CREB gene expression was increased by Yueju, but not ketamine. Taken together, the present study demonstrates for the first time that differential CREB signaling in the hippocampus may contribute to the strain differences in sustaining efficacy of rapid antidepressants.

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Funding support:Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD); Natural Science Foundation of Jiangsu Province (Grant No. BK20140962); Nanjing University of Chinese Medicine Funds for Young Scientists (12XZR04).

Talk: Georgy Bakalkin, Tuesday May 19, 15:00

Epigenome in alcoholism: genetically-regulated trajectories of DNA methylation in human brain

D. Sarkisyan, I. Bazov and G. Bakalkin

The vulnerability to alcohol is determined by genetic, environmental and epigenetic factors. We aim to identify variation in the epigenome that is associated to alcoholism by interrogating DNA methylation sites across the genome. We matched 39 individuals with alcoholism and 47 controls of European descent for age and gender, and analyzed genome-wide methylation of total tissue DNA in the dl-PFC and ventral striatum from all subjects, and neuronal and non-neuronal DNA separately in the dl-PFC of 16 alcoholics and 16 controls, by Illumina's HumanMethylation450 BeadChip assays. Differentially methylated CpGs (DMPs) and CpG regions (DMRs) in alcoholics were identified, and compared between the dl-PFC and ventral striatum. Data will be presented on DMPs / DMRs showing significant effects in both brain tissues, their clustering in modules of inter-correlated CpGs, and association of these modules with alcohol abuse / dependence. In the course of analysis, clusters of CpGs showing highly correlated methylation were identified. Such clusters may serve as a source of epigenetic variation and give insights into the epigenome structure and function. In the promoter of the prodynorphin gene that plays a critical role in addictive disorders, the CpG cluster with highly correlated methylation levels overlaps with the short CpG island. Coherence in methylation at this cluster a) correlates with gene expression across four human brain areas, and b) differ between alcoholics and controls that may underlie changes in transcription of this gene in the addicted brain. In summary, we observed an association between DNA methylation and disease status that overall highlights genes implicated in neuronal functioning.

Dept. Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden.

Talk: Nigel S. Atkinson, Tuesday May 19, 15:30

Using histone marks to identify behaviorally relevant alcohol response genes

Nigel S. Atkinson[1] and Alfredo Ghezzi[1]

Genomic studies often report that a significant fraction of the genome changes expression following exposure to ethanol. Unfortunately, responses important for producing alcohol behaviors can be obscured by this surfeit of changes. To help identify changes important for producing functional behavioral tolerance to alcohol, we exploited the fact that two chemically distinct alcohols produce mutual cross tolerance through a related mechanism. This was demonstrated in detail using the Drosophila *slo* gene as a test case. In flies, the capacity to acquire tolerance to either ethanol or benzyl alcohol has been linked to the *slo* gene, which encodes BK-type Ca^{2+}-activated K^+ channels. Mutations in *slo* block the acquisition of tolerance, sedation with either drug induces *slo* expression, and *slo* induction has been shown to phenocopy tolerance. A survey of the alcohol-induced histone acetylation profile across the *slo* transcriptional control region proved to be an effective way to identify DNA regulatory elements that mediated the alcohol response. Based on the success of this approach, we performed a genomic survey to identify all genes and regions that respond simmilarly to both benzyl alcohol and ethanol. This technique identified a gene network, shown to play important roles in this alcohol response (tested by mutation, RNAi, or transgenic mis-expression). We will report the results of bioinformatic analysis that organized the Drosophila genes into functional networks, which can be functionally tested in Drosophila, and the corresponding human gene networks identified. These regulatory networks extend from transcription factors to synaptic proteins.

1 Waggoner Center for Alcohol & Addiction Research, Department of Neuroscience, The University of Texas at Austin, Austin, Texas, 78712, U.S.A.

Talk: Susan Bergeson, Tuesday May 19, 16:00

Bioinformatics analyses of alcohol-mediated molecular and epigenetic changes reveal age-specific differences in brain and pharmacotherapeutic treatment potential

P.J. Syapin[1], R.G. Agrawal[1], J.A. Owen[1], C.L. Allison[1], P.C. Marquardt[1], Y.M. Al-hasan[1], J.M. Martinez[1], A. Hewetson[1], S. Balaraman[2], R.C. Miranda[2] and S.E. Bergeson[1]

Alcohol-mediated differences in adolescent and adult brain are well documented, yet the mechanisms that underlie the effects and risk of functional brain changes, Alcohol Use Disorders, and eventual treatment efficacy are not understood. We recently reported that adolescent and adult binge alcohol drinking led to age-specific

changes in gene expression of neuroimmune-related pathways in brain. Bioinformatics analyses led us to hypothesize that adult (P70), but not adolescent (P30), mice would respond to pharmacotherapeutic treatment with minocycline, which was tested using Drinking-In-Dark (DID) binge drinking (4 hr/day access to 20% ethanol for 4 days under a reverse-light cycle beginning 3 hrs after dark) and we found that, as predicted, adult, but not adolescent mice, were responsive to the immune-modulatory drug. To understand the mechanisms underlying binge drinking, several epigenetic screens were followed by bioinformatics analyses. Genome-level miRNA expression was assessed by Exiqon high throughput qRT-PCR screens in a 2x2 design (Age x Treatment, n=5/group). To test the hypothesis that miRNA expression changes may be associated with age differences, the known targets of the differentially expressed miRNAs (*mmu-miR-590-3p*, *mmu-miR-20-3p* and *mmu-let-7i*) were analyzed for WebGestalt pathway over-representation, with several neuroimmune-responses meeting significance ($q<0.05$). Genome-wide, chromatin-immunoprecipation screens for epigenetic changes involving H3/4 acetylation, and H3 replacement with the H3.3 variant, showed strong alcohol X age differences. DNA methylation detection also revealed that adult, but not adolescent, DID binge-drinking reduced meDNA levels in brain. Our results indicate that epigenetic mechanisms may play a role in alcohol X age interactions, and potentially affect treatment.

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Funding support: NIAAA grants R21AA021142 (PJS/SEB), U01AA13475 (SEB) and R01AA013440 (RCM).

Talk: Leonard Schalkwyk, Tuesday May 19, 16:30

DNA methylation profiles in Alzheimer disease brains

Lunnon K[1], Smith R[2], Hannon E[1], Mill J[1], Schalkwyk LC[3].

We performed a cross-tissue analysis of methylomic variation in Alzheimer's Disease using samples from four independent human post-mortem brain cohorts. We identified a differentially methylated region in the ankyrin 1 (ANK1) gene that was associated with neuropathology in the entorhinal cortex, a primary site of AD manifestation. This region was confirmed as being substantially hypermethylated in superior temporal gyrus and prefrontal cortex, but not in the cerebellum or whole blood from the same individuals. Neuropathology-associated ANK1 hypermethylation was subsequently confirmed in cortical samples from three independent brain cohorts. This study is, the first epigenomewide association study of AD employing a sequential replication design across multiple tissues and highlights the power of this approach for identifying methylomic variation associated with complex disease.

1 University of Exeter Medical School, Exeter University, Exeter, UK.
2 Institute of Psychiatry, King's College London, London, UK.
3 School of Biological Sciences, University of Essex, Colchester, UK

Talk: Per Jensen, Wednesday May 20, 8:30

Genetics and epigenetics of domesticated social behaviour

Per Jensen[1]

Domestication represents a large-scale evolutionary experiment, where humans have modified the selection pressures on animal populations. We have used behavioural assessment in large populations of dogs for genetic analysis of the mechanisms underlying these effects. For example, the narrow-sense heritabilities of the intensity of problem solving attempts, and the propensity of seeking human assistance, were estimated to 0.32 and 0.23 respectively in a population of laboratory raised beagles, showing a significant genetic component behind variation in human-directed social behaviour. Genome-wide association studies are now undertaken to localize causative genes and mutations.

Furthermore, we study chickens, where the ancestors, the Red Junglefowl, live in small, territorial harem flocks, whereas domestic birds are kept in large single-sex groups, and the ability to survive and function in this environment has been made possible by adaptation of social behaviour. We have used a combination of large-scale inter-crossing and quantitative trait locus (QTL)-analysis, selection of Red Junglefowl, and gene expression analysis to investigate the details of the mechanisms underlying such adaptations. For example, polymorphisms and expression of the vasopressin receptor gene *AVPR1a* may explain parts of the changes in aggression, and a domesticated mutation in the pigmentation related gene *PMEL17* shows pleiotropic effects on feather pecking

as well as on other social behaviour. An ancient mutation in *TSHR*, selected during domestication, affects both reproduction and social behaviour. Our studies also show that epigenetic mechanisms may have played an important role in the fast adaptation and phenotypic radiation commonly associated with domestication.

1 IFM Biology, AVIAN Behaviour Genomics and Physiology Group, Linköping University, 58183 Linköping

Talk: Svante Winberg, Wednesday May 20, 10:00

Stress coping styles in teleost fish – genetic factors and plastic responses to social experience

S. Winberg[1]

Intraspecific variability in behavior has been described in numerous species. Moreover, behavioral traits form divergent clusters, or profiles, and if consistent over time and context, such behavioural profiles have been described as personality or divergent stress coping styles. Animals displaying a proactive coping style respond to a challenge with a high epinephrine and low glucocorticoid release, trigger a fight-flight response, show propensity for social dominance and develop behavioral routines. Reactive individuals, on the other hand, show a freeze-hide response with low epinephrine and high glucocorticoid release, and a tendency to be socially subordinate and to display a more flexible behaviour. Using rainbow trout (*Oncorhynchus mykiss*) strains selected for low (LR trout) and high post-stress cortisol (HR trout) we have shown that LR trout proactive and HR trout reactive. Thus, stress coping style is at least in part heritable. We have also identified similar divergence in stress coping styles in other teleosts, including zebrafish (*Danio rerio*). Coping style also appears to be related to life history traits. In Atlantic salmon (*Salmo salar*) fish leaving the nest early, before consuming the yolk, display more of a proactive coping style whereas those leaving the nest late appear more reactive. Stress coping is also affected by environmental factors, especially factors related to the social environment. Social subordination usually results in a more reactive behavioural profile whereas experience of being socially dominant has the opposite effect. Proactive and reactive stress coping styles is related to differences in brain serotonergic neurotransmission and the expression of genes associated with the brain serotonergic and dopaminergic systems.

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Funding support: The Swedish research council FORMAS, The European Union's 7th Framework Program, Facias

Talk: Elena Jazin, Wednesday May 20, 10:30

Cellular sexual dimorphism of X and Y homologous gene expression in human central nervous system during early male development

Martin Johansson[1]*, Elin Lundin[2]*, Mohammadreza Mirzazadeh[1], Xiaoyan Qian[2], Jonatan Halvardson[3], Elisabeth Darj[4], Lars Feuk[3], Mats Nilsson[2§] and Elena Jazin[1§]

Renewed attention has been directed to the functions of the Y chromosome in the central nervous system during early human male development, due to the recent proposed involvement in neurodevelopmental diseases and cortical ontogeny. *PCDH11Y* and *NLGN4Y* are of special interest, because they belong to gene families involved in cell fate determination and formation of dendrites and axons. Conventional in-situ detection of these genes is not possible; due to the high sequence identity to the X encoded homologs. We used RNA sequencing, immunocytochemistry and a padlock probing and rolling circle amplification strategy, to distinguish for the first time the in-situ expression of X and Y homologs in human embryos, 8-11 weeks. The most striking result; was that the Y encoded genes are expressed in specific and heterogeneous cellular neural subpopulations that rarely express the X homologs. Our findings suggest that a male-specific cellular network may exist in the embryonic central nervous system.

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This work has been submitted for publication to Nature Communications.

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Talk: Galit Shohat-Ophir, Wednesday May 20, 11:00

Social experience modulates group interaction in Drosophila Melanogaster

Galit Shohat-Ophir

Living in a social environment entails diverse types of interactions with distinct characteristics and outcomes, during which animals integrate their internal physiological state with the environmental events, and subsequently choose one action over another to increase their chances of survival and reproduction. Social interaction requires the perception of a socially relevant sensory stimulus, representation of this information in the brain and integration of the stimulus with other behaviorally relevant cues leading to changes in behavior. Using Drosophila melanogaster as a model organism, we have recently shown that we can tap into the fly's natural reward system by exposing flies to a socially rewarding experience (abundant mating events) or the lack of it (sexual rejection), and that this experience modulates the perception of reward value. We identified a molecular signature of this experience in the form of changes in neuropepetide F (NPF) levels and NPF neuronal activity, serving as a representation of internal reward level. To understand how social experience is encoded in the brain we combine genomic analysis methods with newly developed behavior tracking and machine vision technologies, which facilitate the analysis of high content data sets. We are performing cell type specific transcriptomics and RNA editomics to identify the molecular signature of experience within neuromodulatory circuits. This serves as an entry point to study the functional output of this cellular plasticity on reward related behaviors and novel social group interactions associated with rewarding and non-rewarding experiences.

The Mina and Everard Goodman Faculty of Life Sciences Bar-Ilan University, Israel.

Talk: Rui F. Oliveira, Wednesday May 20, 11:30

Neuromolecular mechanisms of social learning in zebrafish

R.F. Oliveira[1,2,3], R.A. Abreu[1,2,3], J.S. Pinho[1,2,3]

The social brain hypothesis postulates that social complexity promotes the evolution of social cognition. In particular the ubiquity of public information in social environments is expected to prompt the evolution of social learning. However, it is still an open question if social learning relies on a newly evolved learning module that deals with this particular type of learning, or if on the contrary the mechanisms underlying social learning are the same as those involved in general purpose learning. It has also been proposed that the difference may rely not on the learning mechanism itself, but rather on attentional processes that make social information available. In this study we address these two questions by: (1) Characterising the behavioural, neural and molecular mechanisms underlying a social and an equivalent asocial learning task in zebrafish; for this purpose an observational fear conditioning paradigm was contrasted with a classical fear conditioning paradigm. (2) Developing a task to study social attention in zebrafish; for this purpose fish observed a pair of non-interacting conspecifics, a pair of interacting conspecifics or an empty tank, and their engagement with the stimuli was measured using a homemade video-tracking system. Behavioural data show similar learning rates in the two learning tasks but higher attention rates towards interacting conspecifics. Brain transcriptome data show differential expression of a small number of genes in the attention task, which are candidates to be involved in attention in zebrafish. These results will be discussed in the scope of the brain modularity hypothesis for social information.

1 ISPA – Instituto Universitário, 2Instituto Gulbenkian de Ciência and 3Champalimaud Neuroscience Program, Lisbon, Portugal,
Country Funding Support: Fundação para a Ciência e a Tecnologia (FCT) grant to RFO (PTDC/PSI-PCO/118776/2010), FCT fellowships to RAA and JP (SFRH/BD/33280/2007 and SFRH/BD/97442/2013, respectively).

Talk: Neema Yazdani, Wednesday May 20, 13:10

Hnrnph1 is a quantitative trait gene for methamphetamine sensitivity

Neema Yazdani[1,2], Clarissa C. Parker[3,4], Ying Shen[5], Michael A. Guido[3], Loren A. Kole[3], Stacey L. Kirkpatrick[1], Jackie E. Lim[3], Greta Sokoloff[3,6], Riyan Cheng[3,7], W. Evan Johnson[5], Abraham A. Palmer[8], Camron D. Bryant[1]

Sensitivity to the locomotor stimulant effects of amphetamines is a heritable trait in mice that may aid in our understanding of the genetic and neurobiological basis of neuropsychiatric disorders involving perturbations in dopaminergic transmission. We previously used short-term selected mouse lines derived from a C57BL/6J (B6) x DBA/2J (D2)-F2 cross to identify a quantitative trait locus on chromosome 11 that was causally associated

with reduced methamphetamine-induced locomotor activity (D2 < B6). We have since replicated this QTL in a standard B6 x D2-F2 cross and used phenotypic analysis of interval specific congenic lines containing various D2-derived segments of chromosome 11 on an isogenic B6 background to uncover a 206 Kb critical interval containing only two protein-coding genes, Rufy1 and Hnrnph1, both necessary for reduced MA sensitivity. Here, we used transcription activator-like effector nucleases (TALENs) to induce small deletions in the first coding exon of Rufy1 or Hnrnph1. Phenotypic analysis of replicate lines heterozygous for the Hnrnph1 deletion recapitulated the congenic phenotype, thus identifying a quantitative trait gene. Transcriptome analysis of B6.D2 congenic (chr.11: 50-60 Mb) striatal tissue followed by pathway analysis revealed perturbations in "glutamate receptor signaling" and "GalphaQ signaling", and identified "Cellular development, nervous system development and function, behavior" as the top network. We hypothesize that Hnrnph1 regulates neurodevelopment of the mesocorticolimbic circuitry, thereby affecting both dopaminergic neuron development and glutamate signaling, and hence the stimulant response to amphetamines. These results will likely have widespread implications for understanding the genetic and neurobiological bases of disorders comprising perturbations in dopamine neurotransmission, including addiction, schizophrenia, ADHD, OCD, and Parkinson's disease.

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Talk: William J. Giardino, Wednesday May 20, 13:30

Genetic Dissection of Extended Amygdala Circuitry Linking Anxiety, Aversion, and Behavioral Arousal

William J. Giardino[1], Tawaun A. Lucas[2], Luis de Lecea[1,2]

The bed nucleus of the stria terminalis (BNST) is a stress-responsive forebrain structure comprised of distinct cellular subgroups expressing numerous neurotransmitters and neuromodulators. Ventral tegmental area (VTA)-projecting BNST neurons are modified by ethanol dependence and contribute to reward-seeking, but tremendous cellular heterogeneity in the BNST has limited understanding of the behavioral profiles associated with genetically-defined BNST subpopulations. We sought to clarify these relationships by performing BNST viral manipulations in male C57BL/6J-background mice expressing Cre under either *Slc32a1* (vesicular GABA transporter [Vgat]) or *Crh* (corticotropin-releasing factor [CRF]) promoters. In parallel VTA studies, mice expressed Cre under *Th* (tyrosine hydroxylase) or *Slc6a3* (dopamine reuptake transporter [DAT]) promoters. Behavioral studies used Cre-dependent viruses encoding fluorophore-tagged Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). DREADDs are mutant G-protein-coupled receptors capable of excitatory (hM3Dq) or inhibitory (hM4Di) signaling via the otherwise physiologically-inert ligand clozapine-N-oxide (CNO). Mice were tested for CNO-induced anxiety-like behaviors, place conditioning, and free-choice CNO drinking. Compared to Cre-positive littermates that received fluorophore-only virus, excitatory BNST-hM3Dq signaling in Vgat-Cre and CRF-Cre mice produced anxiogenic-like states and avoidance of CNO-paired stimuli. Excitatory VTA-hM3Dq signaling supported hyperlocomotion and preference for CNO-paired stimuli. To validate DREADD-specific effects on neural activity, immunohistochemical analyses quantified transcriptional changes in directly-targeted neurons and downstream populations. To outline behaviorally-relevant BNST connectivity, anatomical experiments queried the inputs and outputs of genetically-defined neurons by Cre-dependent retrograde (modified rabies virus) and anterograde (channelrhodopsin-2) tracing strategies. Current studies are investigating BNST interactions with wake-promoting lateral hypothalamic hypocretin neurons and other nodes in the stress-arousal circuitry.

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Funding: NIH F32 AA022832

Talk: Eleanor Hobbs, Wednesday May 20, 13:50

Validation of the candidate risk gene for neuropsychiatric disease *CACNA1C* using a mouse ENU mutagenesis screen

Eleanor Hobbs[1], Valter Tucci[2], Glenda Lassi[2], Greg Joynson[3], Patrick Nolan[1], Michael Parsons[1]

Neuropsychiatric disorders such as schizophrenia and bipolar disorder have a large genetic component with symptoms including hallucinations, disturbed emotional state, cognitive deficits and sleep/circadian disturbances. Genome-wide association studies (GWAS) have identified variants in genes associated with these disorders, including *CACNA1C*, a voltage-gated calcium channel subunit. While the *Cacna1c* null allele is homozygous lethal in mice, conditional and brain-specific knockouts show behavioural defects including increased anxiety. At MRC Harwell, we have used an ENU mutagenesis DNA archive to screen for additional *Cacna1c* allelic variants expressing more subtle and varied behavioural phenotypes. Using this approach, we identified a DNA sample with a missense mutation in the EF-hand region of the gene (responsible for inactivation of the channel). Mice carrying this mutation were rederived and subsequently underwent a battery of behavioural phenotyping tests. In the open-field test homozygous mutants showed decreased anxiety and increased exploratory behaviour (mania), the opposite of what has previously been reported in knockout models. Further tests of anxiety including Elevated Plus maze partially validated these findings. This suggests that this may be a gain-of function mutation and is our basis for further characterisation. Using inactivity as a correlate of sleep, we found that these mice had a shorter sleep latency which is interesting as *CACNA1C* has also been implicated in GWAS for narcolepsy. We now plan to investigate the molecular basis of this phenotype using calcium imaging in vitro. These results, together with the observed phenotypes, could validate *CACNA1C* as a risk gene for bipolar disorder and sleep disturbances.

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Funding support: Medical Research Council (UK); Brain and Behavior Research Foundation; Istituto Italiano di Tecnologia.

Talk: Petronella Kettunen, Wednesday May 20, 15:00

Using zebrafish to study the role of oxytocin in social behavior

Petronella Kettunen[1]

The zebrafish is a fairly novel model system that is particularly suitable for psychiatric research due to the developed behavioral tests, ease of pharmacological treatment and the available mutated lines of genes involved in human diseases and disorders. Due to their strong tendency to socialize in shoals, zebrafish serves as a good model to study social behavior. Isotocin, the fish homolog of oxytocin, and its receptor exist in the zebrafish. In this project, we are studying the role of istocin on social behavior in adult zebrafish by the use of pharmacological treatment and behavioral tests of social preference and sociability. Our initial findings have confirmed that isotocin is regulating social behavior in zebrafish. In a first test, fish intraperitoneally injected with the nonpeptidergic specific OXTR antagonist L-368,899 decreased their social preference compared to fish IP injected with the vehicle. This indicates that endogenous oxytocin is involved in social preference in fish. In a second test of sociability, we have used the NMDA blocker MK-801 that has previously been used as an autism model in rodents. In this test, the density of shoals of adult zebrafish treated with MK-801 was decreased. Moreover, injections of isotocin rescued the reduced sociability induced by MK-801. These findings show promise for future explorations of the network underlying social behavior in the zebrafish.

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Talk: Sietse F. de Boer, Wednesday May 20, 15:30

The promise and perils of oxytocin as neurochemical mediator of sociality: insights from rodent studies

Sietse F. de Boer

Ever since that Pedersen (1979) found that centrally administered oxytocin (OXT) promoted maternal nurturing in virgin female rats, the scientific understanding of the many roles this brain nonapeptide plays in virtually all aspects of mammalian social life has advanced tremendously. In addition, impaired brain OXT-ergic signaling

has been firmly implicated in several human neuropsychiatric disorders associated with social deficits, impulsivity and excessive aggression. Hence, a focus of our research revolves around elucidating the precise role of OXT on social aggressive behaviors in feral male Wild Type Groningen (WTG) rats. This rat strain has proven to be very suitable to investigate the neurobiological roots of intermale aggression and violence, allowing us to explore neuromolecular mechanisms linking (ab)normal aggressive behavioral phenotypes with endogenous OXTergic activity. Our ethopharmacological studies have clearly shown that enhancement of brain OXTergic function, using both intraventricular, intracerebral, and even intranasal administration routes, produced marked anti-aggressive and pro-social affiliative effects that are dose-dependent, behavior- and receptor-selective and long-lasting. Although the underlying mechanisms for the putative direct OXT nose-to-brain transport still needs to be elucidated, intranasal OXT administration was shown to increase the endogenous activity of OXT neurons in hypothalamic regions. Interestingly, these behavioral changes are strongly moderated by the individual's basal level of aggressiveness, suggesting an inverse relationship between trait-like aggressiveness and endogenous brain OXTergic signaling. In situ hybridization and receptor autoradiography have indeed revealed a significantly lower OXT mRNA expression in the paraventricular nucleus, but not in the supraoptic nucleus, of excessively aggressive/violent rats as compared to both low and medium-high normal aggressive ones. These findings strongly support the hypothesis that variations in the structural and functional properties of brain oxytocin-ergic circuits may give rise to individual differences in aggressiveness and/or coping with conflict. From a translational medicine perspective, the data support the emerging notion that OXT may be a promising target for treatment approaches for mental disorders characterized by excessive aggression and social dysfunction

Department of Behavioral Physiology, University of Groningen, The Netherlands

Talk: Lars Westberg, Wednesday May 20, 16:00

Variants of the oxytocin receptor gene and human social behaviors

Lars Westberg[1]

Tentative evidence from mainly small to moderate-sized samples indicates that polymorphisms of the oxytocin receptor gene (*OXTR*) have impact on human social behaviors and on increasing the risk of social deficits. In a series of studies we have evaluated the most promising variants in a number of large cohorts assessed for various social behaviors. We recently reported associations between a genetic variant in the *OXTR*, rs7632287, and different measures of pair-bonding behavior in two large independent cohorts of women. These findings are well in line with previous knowledge from females of monogamous and nonmonogamous vole species. The same variant also associated with face memory and related amygdala activation, in a recent imaging genetics study. These results support previous mice experiments showing that oxytocin receptor function in amygdala is essential for social recognition. Furthermore, in two independent samples we also revealed associations between an *OXTR* variant, rs4564970, and alcohol-induced aggression, measured experimentally and by self-assessment, respectively. In a recent study of aggression we investigated eight *OXTR* variants in approximately 2300 18-year-old twins self-assessed for aggressive and antisocial behaviors with two different instruments. Intriguingly, two independent SNPs, again rs4564970 and rs7632287, were associated with both measures of aggressive and antisocial behaviors in boys. Intriguingly, in an independent sample the same rs7632287 genotype was again associated with higher scores on a similar measure of aggression. Taken together, these findings indicate that at least rs7632287 located 3' of *OXTR* influences various aspects of human social behaviors.

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Talk: Erika Roman, Thursday May 21, 10:00

Risk-related behaviors and propensity for excessive alcohol intake

Erika Roman[1]

Risk assessment and risk taking versus shelter seeking are evolutionary conserved behaviors of relevance for decision-making processes, and have been implicated in the multifaceted construct of impulsivity. Outbred Wistar rats originating from the Wistar Institute and the Zentralinstitut für Versuchstierzucht in Hanover are likely different in their genetic makeup even if data on this topic are sparse. When studying rats of different origin, analyses reveal differences in behavioral profiles, as assessed in the multivariate concentric square field™ (MCSF) test, acquisition of voluntary alcohol intake and response to pharmacological treatment with naltrexone.

Moreover, within a population of Wistar rats from the same supplier, subgroup-dependent differences in risk-related behaviors were associated with propensity for higher alcohol intake and differences in in vivo dopamine dynamics in the dorsal striatum, an area hypothesized to be involved in the shift from drug use to addiction. Also some selectively bred alcohol-preferring and alcohol-nonpreferring rodent lines display differences in risk-related behaviors within pairs. Finally, recent data indicate that when selecting zebrafish for extreme differences in risk-taking behavior differences in the expression of the dopamine D2 receptors and delta opioid 1b receptor were found. How these differences relate to drug-related behaviors remains to be elucidated. These results underscore the usefulness of profiling innate differences and subgroup-dependent differences in risk-related behaviors for a deeper understanding of the neurobiological basis for risk-related behaviors and its association with alcohol intake in an attempt to understand factors that drive excessive alcohol intake and propensity for addiction.

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Talk: Nicholas Grahame, Thursday May 21, 10:30

High Impulsivity, poor response inhibition, and prevalent habitual behavior associate with genetic differences in volitional alcohol intake.

Nicholas Grahame, David O'Tousa, and Liana Matson, Indiana University-Purdue University, Indianapolis, Indiana, USA

A genetic predilection towards alcoholism is likely composed of a constellation of phenotypes, some more prevalent in given lineages than others. Nonetheless, a consistent thread of comorbidity with disorders characterized by impulsivity and impaired response inhibition emerges from twin and adoption studies of alcoholism. Mice selectively bred to drink alcohol, to the extent that they recapitulate aspects of this disorder, should allow dissection of psychological mechanisms associating with increased drinking behavior. Indeed, previous studies from our lab demonstrated greater cognitive impulsivity in High Alcohol Preferring (HAP lines as compared with Low Alcohol Preferring (LAP) lines. Here, we present new data on additional constructs that may be related to impulsivity: response inhibition, as measured by a differential reinforcement of low rates of responding (DRL) task, and transition to habitual behavior, as measured by continued seeking of a reinforcer after it has been devalued. We used replicated selected lines to assure that genetic differences were related to the selection phenotype, 2-bottle choice alcohol consumption. We observed that although both HAP and LAP lines were able to inhibit behavior under a DRL schedule, HAP mice showed consistently higher response rates, resulting in a higher number of omitted reinforcers, than LAP mice, indicating difficulties with response inhibition. In an operant setting, we observed that HAP lines shift to habitual, devaluation-resistant behavior very rapidly compared to LAP lines. Together, these findings are consistent with recent theories indicating that addiction associates with poor response inhibition and elevated susceptibility towards habitual, rather than outcome-based instrumental learning.

Talk: Chiara Giuliano, Thursday May 21, 11:00

Compulsive alcohol-seeking behavior is attenuated by inhibiting μ-opioid receptors.

Giuliano C[1], Goodlett CR[2], Everitt BJ[1]

One of the most challenging aims in pre-clinical research is to develop animal models that can provide valuable and reliable tools with which to investigate specific aspects of neuropsychiatric disorders relevant to pharmacotherapeutics. One characteristic feature of addiction is that drug-seeking behavior is triggered and maintained by drug-associated environmental stimuli. Here alcohol-preferring (P) rats were trained to respond instrumentally for alcohol under a second-order schedule of reinforcement, in which a prolonged period of alcohol-seeking behavior was maintained by contingent presentation of an alcohol-associated conditioned reinforcer followed by 20-min free-access to alcohol. An additional feature of drug addiction is the loss of control over drug-seeking and taking despite adverse or negative outcomes. Here we further adapted a seeking-taking chained schedule of alcohol intake in which instrumental seeking responses in P rats resulted either in the opportunity to drink alcohol, or in unpredictable mild foot-shock punishment. In a subgroup of animals, alcohol-seeking persisted despite the unpredictable, intermittent delivery of 0.45mA foot-shock punishment. That same subgroup of animals also showed increased alcohol-seeking behavior under extinction-conditions and increased motivation for alcohol measured under a progressive-ratio schedule for alcohol. Seeking behavior under both tasks was also challenged by treatment with the novel selective μ-opioid receptor antagonist GSK1521498,

which reduced both compulsive and non-compulsive alcohol-seeking behaviors, as well as alcohol drinking. Taken together with our earlier work showing that GSK1521498 also prevented cued cocaine- and heroin-seeking, these data indicate the great potential for selective μ-opioid receptor antagonism in relapse prevention and abstinence promotion across addictive drug classes.

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Talk: J. David Jentsch, Thursday May 21, 11:30

Genetic analyses of impulsivity and motivated behavior as addiction-relevant traits

J. David Jentsch[1]

Historically, a number of biobehavioral traits have been shown to segregate with substance use disorders, particularly heightened impulsivity and sensitized incentive motivation. Recent data suggest that this phenotypic association may result from the fact that impulsivity and motivational tone are heritable risk factors for substance use disorders, possibly through influencing the initiation of drug-taking behavior, or its escalation with extended experience with the drug. The concept that heritable variation in impulsivity or incentive motivation is a susceptibility factor for the initiation of drug-seeking was tested using an inbred mouse reference panel (the hybrid mouse diversity panel). Phenotypes indicative of impulsivity (reversal learning), incentive motivation (operant responding for a sweet reward) and drug-taking (intravenous cocaine self-administration) were assessed in large numbers of strains (~100, ~75 and ~50, respectively). Analyses showed that all are heritable traits and that impulsivity, but not incentive motivation, is genetically correlated with drug self-administration behaviors. Genome-wide association revealed non-overlapping quantitative trait loci for the three traits. Weighted gene co-expression network analyses of brain gene expression traits identified eigengenes with expression that correlated with the behavioral traits, and transcripts expressed from the linked quantitative trait loci were involved in correlated gene expression modules. These studies underscore the potential of systems genetic approaches to uncover novel biological mechanisms giving rise to the segregation between high impulsivity and elevated drug-taking behaviors.

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Talk: Zeiss, Thursday May 21, 12:30 (Lunch Seminarium)

Tissue clearing allows you to image deep into large biological samples such as brains, tissue sections, embryos, organs, spheroids or biopsies. You can use its enhanced optical penetration depth to capture fluorescent signals of whole organs. This makes clearing a promising technique when, for example, investigating neuronal networks in mouse brains.

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Talk: Christian Rosenmund, Thursday May 21, 13:00

Glutamate/GABA co-release on a vesicular level in mammalian neurons

Johannes Zimmermann, Melissa Herman, Christian Rosenmund

Co-release of two or more classical neurotransmitters from the same neuron seems to be quite common throughout the nervous system. However, the co-release of glutamate and GABA – the two major excitatory and inhibitory NTs – has not been thoroughly analyzed on a vesicular level. In this talk we address whether GABA and glutamate can be released from the same vesicle. We performed recording of postsynaptic events in autaptic GABAergic neurons cultured from the striatum, which were exogenously expressing the vesicular glutamate transporter VGLUT3. We found that action potentials in GABAergic neurons expressing VGLUT3 evoked mixed postsynaptic currents (PSC) mediated by both GABA and glutamate release. Using analysis of decay kinetics of both spontaneously release miniature PSCs (mPSC) and asynchronous events evoked in Sr2+, we suggest that the quantal events underlying the evoked mixed PSC included vesicles containing both glutamate and GABA. We

tested for synergistic effects of GABA loading when glutamate was present in the vesicle. Neurons expressing VGLUT3 did not exhibit an increase in vesicular GABA content, measured by the mPSC size in presence of glutamate receptor antagonist NBQX. Glutamate release from GABAergic neurons did not alter the expression level of postsynaptic surface AMPA receptors, as exogenous kainate application evoked similar currents in control GABAergic cell and those expressing VGLUT3. We report, however, that synaptic input of "purely" glutamatergic neurons to striatal GABAergic neurons expressing VGLUT3 impedes detection of glutamate corelease induced by stimulation of the GABAergic neuron, probably by drawing away AMPA receptors to glutamatergic synapses. Thus co-release of glutamate and GABA is defined by co-expression of the respective vesicular transporters, but the postsynaptic detection is also dependent on the proper equipment of postsynaptic receptors.

Neuroscience Research Center, Charite Medical School, Berlin, Germany

Talk: Louis-Eric Trudeau, Thursday May 21, 13:30

Role and topography of glutamate release sites in dopamine neurons

L-E Trudeau[1,2], GM Fortin[1], M-J Bourque[1], Z Saneei[1], C Pacelli[1], R Koerich Varaschin[1], N Giguère[1], M Brill[1], S Singh[3], PW Wiseman[3]

Dopamine neurons are key players in brain circuits involved in motor control, motivated behaviors and cognitive functions. Recent work identifying glutamate as a second neurotransmitter in a subset of dopamine neurons, mainly located in the ventral tegmental area, has triggered a reconsideration of the roles of dopamine neurons in the brain as well as of the structural organization of these neurons. In his presentation, Dr. Trudeau will present recent work suggesting that one of the key roles of glutamate release by dopamine neurons is to promote their growth and survival during development. Evidence will also be presented to show that glutamate and dopamine release sites are topologically segregated, suggesting the existence of a complex triage and axonal distribution of vesicular proteins in these double-phenotype neurons.

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Country funding support: Canadian Institutes of Health Research, MOP-106556, CANADA

Talk: Stefano Pupe, Thursday May 21, 14:00

New subpopulations within the brain reward system

Åsa Wallén-Mackenzie[1] and Stefano Pupe[1]

The brain reward system is at core of the brain systems that regulate and mediate motivated and goal-directed behaviour and it is thus important for everyday life in most species. In humans, these behaviours can be dysregulated in such a way that it contributes to psychiatric disorders. We are interested in identifying and charaterizing subpopulations within the brain reward system of the mouse that are not based only on neurotransmitter identity but also on anatomical localization and projection target areas. We have recently identified such subpopulations within the ventral tegmental area (VTA) and the subthalamic nucleus (STN) that we have found contributes to various kinds of reward responses in mice. We will describe some of these findings that, based on behavioural and electrophysiolgical optogenetics in mice, we believe may be of interest also for neuronal function and dysfunction in humans.

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Talk: Salah El Mestikawy & Stephane Jamain (shared talk), Thursday May 21, 14:30

VGLUT3 : from glutamate-cotransmission to pathophysiology of psychiatric disorders

S. El Mestikawy[1,2,5], S. Jamain[3,4,5], D.Y. Sakae[1,2], F. Marti[1,2], A. Henrion[3,4,5], F. Vorspan[5,6,7], F Bellivier[5,6,7]

Glutamate is the major excitatory neurotransmitter in the brain. Before its exocytotic release, glutamate is accumulated into synaptic vesicles by proton-driven transporters named VGLUT1-3. VGLUT1 and VGLUT2 are expressed by cortical and subcortical glutamatergic neurons, respectively. VGLUT1 and VGLUT2 are functional and anatomical markers of canonical glutamatergic neurons. In contrast, VGLUT3 is found in discrete

populations of neurons releasing other transmitters than glutamate such as: cholinergic interneurons from the dorsal and ventral striatum, subpopulations of GABAergic basket cells from the hippocampus or the cortex and serotoninergic neurons from raphe nuclei. We have recently established that VGLUT3 and the vesicular acetylcholine transporter (VAChT) are present on the same synaptic vesicles. As a consequence, VGLUT3 accelerates vesicular filling and release of acetylcholine in striatal cholinergic interneurons (also named TANS). Through this new presynaptic regulatory mechanism (named: vesicular synergy), glutamate accelerates striatal cholinergic vesicular accumulation. VGLUT3 fulfills (at least) 2 functions in TANS: i) it increases cholinergic tone and ii) it provides these cholinergic neurons the ability to signal with glutamate. Mice lacking VGLUT3 (VGLUT3-KO) show a decreased cholinergic transmission. We also observed that VGLUT3 regulates locomotor activity and sensitivity to substance of abuse such as cocaine. Moreover, VGLUT3 is present in GABAergic and 5-HT terminal of limbic areas such as the hippocampus. Taken together, these observations suggest that VGLUT3-positive terminals in the nucleus accumbens and in limbic areas could play a crucial role in psychiatric disorders such as addiction, anxiety and mood regulation.

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Talk: Patrick Martin Nolan, Thursday May 21, 15:40

Loss of function of the microtubule severing enzyme *KATNAL1* underlies defects in behaviour, neuronal migration and neuronal morphology.

Gareth Banks[1], Glenda Lassi[2], Federico Tinarelli[2], Thomas Lawson[1], Henrik Westerberg[1], Lee B Smith[3], Valter Tucci[2], Patrick M Nolan[1].

Intellectual disability (ID) is a generalised disorder characterised by impairments in cognitive and intellectual functions and in adaptive behaviours. With recent advances in genomics and genetic analysis there has been an explosion in the number of potential causative genes of ID. While knowledge of these genetic factors is highly informative in our understanding of the condition, tools such as animal models must be utilized to fully characterise the mechanisms through which specific gene variants contribute to ID. A recent study has suggested that the microtubule severing enzyme *Katnal1* may be a risk gene for ID, although it is unclear at this time how disruptions to *Katnal1* function alter neural mechanisms leading to the development of the disorder. To investigate this, we have identified and characterised a mouse line carrying a loss of function allele in the *Katnal1* gene. We show that *Katnal1* mutant mice have a range of behavioural deficits including in biological rhythms, sleep and learning and memory dysfunctions. Furthermore we demonstrate a number of gross morphological abnormalities in the brains of *Katnal1* mutant mice including substantially increased ventricular size. Moreover, we have established that defects in neuronal migration and morphology which may underlie these phenotypes. From this data we conclude that *Katnal1* is indeed a risk gene for ID and highlight its role in neuronal development.

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Funding support: Medical Research Council.

Talk: Sihhui Huang, Thursday May 21, 16:00

Domestication by selecting for tameness increases adult hippocampus neurogenesis in middle and temporal hippocampus in foxes

Shihhui Huang[1,2,3], Lutz Slomianka[2], Andrew J. Farmer[4], Anastasiya V. Kharlamova[5], Rimma G. Gulevich[5], Yury E. Herbeck[5], Lyudmila N. Trut[5], David P. Wolfer[1,2,3] and Irmgard Amrein[2,3]

Several earlier findings suggest that the regulation of adult hippocampal neurogenesis (AHN) might be modified during domestication. However, there is no laboratory rodent model which can allow us to compare the change of AHN in different degrees of domestication. Here we compare AHN along the hippocampal septo-temporal

axis in farm-bred silver foxes selected for tameness in comparison to unselected foxes. We used design-based stereological methods to estimate the numbers of proliferating cell (Ki67+) and young neurons (doublecortin, DCX+) in defined septal and temporal regions.

Higher neurogenesis is observed in tameness-selected foxes, notably in an extended subgranular zone of the middle and temporal compartments of the hippocampus. Increased neurogenesis is negatively associated with aggressive behavior. Across all animals, strong septo-temporal gradients are observed, with higher numbers of proliferating cells and young neurons relative to resident granule cells in the temporal than in the septal hippocampus. The opposite gradient is found for the ratio of DCX/ Ki67 positive cells. When tameness-selected and unselected foxes are compared to rodents and primates, proliferation is similar, while the number of young neurons is higher. The difference may be mediated by an extended period of differentiation or higher rate of survival.

In conclusion, our results indicate that selection of foxes for a single behavioral trait key to domestication, i.e. genetic tameness, is accompanied by global and region-specific increases in neurogenesis.

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Talk: Silvia Poggini, Thursday May 21, 16:20

The double outcome of antidepressant treatment depends on the quality of the living environment

Silvia Poggini[1], Silvia Alboni[2], Nicoletta Brunello[2], Francesca Cirulli[1], Igor Branchi[1].

Antidepressants, and in particular serotonin selective reuptake inhibitors (SSRIs), represent the standard treatment for Major Depression (MD). However, their efficacy is variable and incomplete. A recent hypothesis, named the Undirected Susceptibility to Change, posits that SSRIs may not affect mood *per se* but, enhancing neural plasticity, may render the individual more susceptible to the influence of the environment. To assess this hypothesis, we treated C57BL/6 adult male mice with either fluoxetine (FLX) or vehicle (VEH) for 3 weeks while exposing them to either an enriched or a stressful environment, following a chronic stress period aimed at inducing a depression-like phenotype. Endophenotypes of MD considered were liking- and wanting-type anhedonia, cognitive bias and corticosterone and BDNF levels. Our findings showed that in the enriched environment, FLX mice displayed a significant reduction in wanting-type anhedonia and a higher number of "optimistic" responses in the cognitive bias test compared to VEH. By contrast, in the stressful condition, FLX mice displayed a significant increase in liking- and wanting-type anhedonia. With regard to the neuroendocrine endpoints, we found that FLX mice exposed to a favorable environment display lower corticosterone levels and higher hippocampal and hypothalamic BDNF levels. Instead, in the stressful condition, FLX mice had a significant increase in corticosterone levels compared to VEH. The present results show that the outcome of fluoxetine treatment depends on the quality of the environment and fluoxetine amplifies the influence of the environment on the individual, reducing depression-like behavior in a favorable environment but exacerbating it in stressful conditions.

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Talk: Laurence Coutellier, Thursday May 21, 16:40

Abnormal juvenile maturation of the GABAergic system in the prefrontal cortex of Npas4 deficient mice

L Coutellier[1]

Disruption of juvenile GABAergic maturation of the prefrontal cortex (PFC) is associated with cognitive and emotional deficits that characterize psychopathologies including schizophrenia and mood disorders. These disorders are known to have a strong genetic component. We thus suggest that identifying the genetic

contributors to cortical GABAergic maturation could help us understand such disorders. Here we show that *Npas4* could be such a genetic factor. We first show using RT-qPCR techniques in PFC tissue of C57Bl6/j mice, that Npas4 is preferentially expressed in the male juvenile PFC, while in females Npas4 expression reaches its highest level during mid-adulthood. We then show in transgenic mice, that Npas4 deficient mice have impaired PFC GABAergic neurotransmission during the juvenile period: in males, low expression of GAD67 was associated with increased expression of $GABA_A$ receptor; in females, $GABA_A$ receptor expression was reduced. These prefrontal GABAergic abnormalities were associated with PFC-dependent cognitive function deficits that were rescued by a chronic treatment with a GABA enhancer during the juvenile period. This treatment also restored normal expression of some of the PFC GABAergic markers. Our data indicate for the first time that Npas4 could be a genetic factor that contributes to the juvenile maturation of the PFC GABAergic system in a sex-dependent way. As such, *Npas4* could also contribute to the susceptibility to neuropsychiatric disorders that are characterized by prefrontal GABAergic dysfunctions (i.e. schizophrenia; mood disorders). Further analyses in tamoxifen-inducible conditional knockout mice will be conducted to verify the significant contribution of *Npas4* during the juvenile period.

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Talk: Yehuda Ben-Shahar, Friday May 22, 8:30

The genetics of neuronal and behavioral homeostasis

Y Ben-Shahar[1,2]

Neurons have to regulate ionic fluxes across their plasma membrane to maintain their excitable properties under varying environmental conditions. This fundamental physiological property of neurons is essential for the expression of adaptive behaviors by the nervous system. My laboratory is interested in identifying the molecular, genetic, and evolutionary principles that drive and maintain neuronal homeostasis and its relationship with behavioral phenotypic plasticity and robustness. To achieve our goals, we use the power of *Drosophila* genetics to identify genome-level architectures, and specific molecular mechanisms, that drive and maintain neuronal and behavioral homeostasis and plasticity. Here I will discuss our recent discovery of a novel post-transcriptional molecular process that regulates the homeostatic response of neurons to stress by modulating the transcript levels of ion channels that affect neuronal excitability. This evolutionary conserved mechanism enables flies to maintain intact neuronal and behavioral functions under environmental stress conditions. Understanding how neuronal and behavioral phenotypic plasticity are encoded in animal genomes could have a profound impact on studies of the evolution of behavioral traits, provide a better theoretical and experimental models for linking population genetic variability with phenotypic distributions, and could lead to novel insights from genome-wide association studies of behavior in health and disease.

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Talk: Pietro Cottone, Friday May 22, 10:00

High trait impulsivity predicts food addiction-like behavior in the rat.

P. Cottone[1]

Impulsivity is a behavioral trait frequently seen not only in drug-addicted individuals but also in individuals who pathologically overeat. However, whether impulsivity predates the development of uncontrollable feeding is unknown. In this study, we hypothesized that a high impulsivity trait precedes and confers vulnerability for food addiction-like behavior. For this purpose, we trained *ad libitum*-fed male Wistar rats in a differential reinforcement of low rates of responding (DRL) task to select Low- and High-impulsive rats. Then, we allowed Low- and High-impulsive rats to self-administer a highly palatable diet (*Palatable*) or a regular chow diet (*Chow*) in 1-h daily sessions, under fixed ratio (FR) 1, FR3, FR5, and progressive ratio (PR) schedules of reinforcement. In addition, we tested the compulsiveness for food in Low- and High-impulsive rats by measuring the food eaten in the aversive, open compartment of a light/dark conflict test. Finally, we measured the expression of the transcription factor ΔFosB in the nucleus Accumbens (NAcc) shell and core, a marker for neuroadaptive changes following addictive drug exposure. The data obtained demonstrate that impulsivity is a trait that predicts the development of food addiction-like behaviors, including: (i) excessive intake, (ii) heightened motivation for

food, and (iii) compulsive-like eating, when rats are given access to highly palatable food. In addition, we show that the food addiction phenotype in high impulsive subjects is characterized by increased expression of the transcription factor ΔFosB in the NAcc shell. These results reveal that impulsivity confers an increased propensity to develop uncontrollable overeating of palatable food.

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Talk: Ida Nilsson, Friday May 22, 10:30

The anorexia of the *anx/anx* mouse is associated with hypothalamic degeneration and mitochondrial dysfunction

Ida AK Nilsson[1,2], Charlotte Lindfors[1,2], Tomas Hökfelt[3], Martin Schalling[1,2]

The *anx/anx* mouse is a unique genetic model for the core features of Anorexia Nervosa, i.e. starvation and emaciation. The *anx* mutation arose spontaneously in 1976 (1). While born without clear pathology, the homozygote mice eat approximately half as much as their healthy siblings and subsequently become starved and die by three weeks of age. The *anx/anx* mouse has in several studies been documented to possess aberrances in neuropeptidergic and -transmitter systems originating in the hypothalamus e.g. AGRP/NPY and POMC/CART (summarized in (2)). In our recent studies, we concluded that the anorexia of this mouse is related to a hypothalamic inflammation and/or degeneration, shown by among others activation of microglia, neuronal expression of MHC class 1 and caspase 6 (3; 4). It appears as if the *anx/anx* mice possess an injury in the food intake regulating systems that shuts down the signaling of hunger. This seems to occur due to a down regulation of a gene called *Ndufaf1* resulting in mitochondrial dysfunction (5). This mitochondrial dysfunction gives rise to increased levels of ROS and a cellular energy deficiency, a process that resembles what is known to occur in other neurodegenerative diseases, e.g. Parkinson's. Due to the expression of a specific type of ATP-sensitive channel by Arc neurons the energy deficiency and increased ROS seems to put the neuron in a hibernation state which if maintained for a too long period can result in neurodegeneration.

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Talk: Andrew Hardaway, Friday May 22, 11:00

Nociceptin signaling modulates the expression of limited access binge eating

JA Hardaway[1,2,3], JA Sugam[1,2], M Kim[1,2], CM Bulik[3,4,5], TL Kash[1,2]

Binge eating disorder (BED) is the most common eating disorder that afflicts between 2-3% of both males and females over their lifetime. BED is characterized by persistent episodes of binge eating, the consumption of an excessive amount of food paired with a sense of loss of control. Similar patterns of binge-like feeding can be generated in mice using pharmacological, behavioral, or circuit level strategies. For example, the injection of nociceptin (NOC) peptide into the brain produces a significant increase in feeding, but the functional requirement of this pathway during palatability driven binge eating is unknown. We used a behavioral model of BED where mice were provided with intermittent 1-hour daily access to a highly palatable and fat-rich food (HFD). Intermittently fed mice will eat significantly more in this session than animals provided with continuous 24-hour exposure, demonstrate rapid onset consumption during the first 10 minutes, and slowly escalate

their binge intake over several weeks. Treatment with the NOC receptor antagonist SB 612111 significantly reduces both the maintenance and induction of intermittent HFD consumption. Using NOC reporter mice, we determined that NOC neurons of the central amygdala (CeA) are activated following intermittent access binging. We targeted NOC^{CeA} neurons using the inhibitory designer receptors exclusively access by designer drugs (DREADDs), hM4D. Pharmacogenetic inhibition of NOC^{CeA} neurons significantly and selectively reduces HFD intake. We hypothesize that central amygdala NOC neurons and NOC receptor signaling may represent an important node for binge eating and an intriguing target to study for the treatment of BED respectively.

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Talk: Lora Heisler, Friday May 22, 11:30

Subset of Pomc Peptides Controlling Ingestive Behavior and Body Weight

Luke K. Burke[1,2,3], Barbora Doslikova[3], Mark L. Evans[2], Lora K. Heisler[1]

Obesity is one of the global healthcare challenge of the 21st century. The common underlying cause of obesity is a dysregulation of the energy balance equation in which more energy is consumed than is energetically required, and the excess energy is consequently stored, typically as fat. Signals relaying information regarding energy needs and availability are integrated within the brain to influence body weight. Central among these integration nodes is the brain pro-opiomelanocortin (Pomc) peptides, perturbations of which disrupt energy balance and promote severe obesity. Here we transform genetically programmed obese male mice lacking Pomc with increased appetite and reduced physical activity into lean, healthy mice via restoration of Pomc function within a small subset of cells within the arcuate nucleus of the hypothalamus (ARC). Remarkably, restoring Pomc function in the equivalent obese female mice does not produce the same metabolic transformation. Although females correct their appetite with restored Pomc capability, they have significantly reduced energy expenditure, remain physically inactive and develop obesity. These results identify an unpredicted sex difference in the way energy is regulated and show that the mechanistic underpinnings driving this large sex difference in energy expenditure is accounted for by a small population of brain Pomc peptides. This may have broad implications for the strategies utilized to combat and reverse obesity.

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This work was supported by the Wellcome Trust (Grants WT081713 and WT098012).

Talk: Palle Dunn Rohde, Friday May 22, 13:00

Functional Insight From Fruit Flies on Human ADHD Candidate Genes

PD Rohde[1,2,3,4], D Demontis[3,4], SMN Arvidson[5], LS Madsen[5], V Loeschcke[2], P Sørensen[1], A Børglum[3, 4] & TN Kristensen[5]

Attention deficit hyperactivity disorder (ADHD) is a psychiatric disorder emerging in early childhood with an average prevalence rate of 5% in children and 3.7% in adults. ADHD is characterized by inattention, impulsivity and hyperactivity. This, combined with educational and social dysfunctions, and increased risk of mental comorbidities, makes ADHD a disorder with high individual and societal costs. We use *Drosophila melanogaster* as a model to investigate the phenotypic consequences of gene disruption of 14 genes with human orthologs, selected by their proposed contribution to increased risk of developing ADHD. We use *Minos* mutants, where target genes have been disrupted by the *Minos* transposable element, to test the effect on locomotor activity. By measuring the distance traveled, we find disparity in locomotor activity between control and *Minos* mutants. Impaired dopamine system underlies the majority of ADHD symptoms, and effective treatment is achieved with amphetamines. We fed flies with either 1.5 mg/ml dexamphetamine dissolved in 5% w/w sucrose or a 5% w/w sucrose solution. Treatment with dexamphetamine increased activity of controls and some *Minos* lines, and decreased activity levels for other mutants. Decreased activity level, when treated with dexamphetamine, is seen when using other ADHD animal models. Our findings suggest involvement of the proposed candidate genes

in hyperactivity in *D. melanogaster*, providing functional evidence for their association with ADHD. Additional studies investigating conditional gene inactivation using UAS-GAL4 systems will further elucidate the importance of the investigated genes.

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Talk: Zhengzheng Sophia Liang, Friday May 22, 13:20

Transcriptomic analysis of allelic imbalance in the mouse olfactory system

ZS Liang[1], SC Munger[2], N Raghupathy[2], DW Logan[1]

Parent-of-origin allelic bias, the epigenetically regulated preferential expression of the paternally- or maternally-derived allele of a gene, is known to influence postnatal social behaviour in mammals. The olfactory bulb (OB) and the major olfactory epithelium (MOE) are important relays in the sensory circuitry that mediates behaviour in mice. We hypothesize that the olfactory system is an unexplored and promising target for parental allelic bias in the nervous system and influences neurodevelopment and behaviour in mammals. We have examined the transcriptomes of the OB and MOE, to identify genes that display allelic expression bias as a function of their parent-of-origin. We used reciprocal crosses of two distantly related inbred mouse strains, CAST/EiJ and C57BL/6J, to differentiate between parent-of-origin and strain-of-origin effects on allelic expression, using deep RNA sequencing. The expression of over 10,000 genes was quantified, resulting in the identification of 44 candidate genes with reproducible and reciprocal parent-of-origin biased expression patterns. Approximately have are genes that have not been previously described as having allelic imbalance. We will further describe the production and initial phenotyping of a mouse line lacking a promising candidate gene from this study. By investigating the behaviour of mice with the mutant allele inherited from the mother compared with the father, we can assess the influence of parental controlled gene expression in the brain.

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Talk: Michael Parsons, Friday May 22, 13:40

Short-circuit: Characterization of a transcription factor that activates a novel circadian transcriptional axis

Michael J. Parsons[1], Marco Brancaccio[2], Siddharth Sethi[1], Elizabeth S. Maywood[2], Rahul Satija[3], Jessica Edwards[1], Nicola J. Smyllie[2], Chris Esapa[1], Johanna E. Chesham[2], Michelle Simon[1], Ann-Marie Mallon[1], Michael H. Hastings[2], Patrick M. Nolan[1]

Circadian rhythms are daily cycles that are controlled by a central hypothalamic pacemaker, the suprachaismatic nucleus (SCN), that regulate both physiological and behavioral traits. Disruptions in circadian rhythms lead to numerous pathologies, including mental disorders and cognition deficits. Temporal regulation of these biological processes is managed in part by changes to the 24 hour transcriptional profile, which is governed by the interaction of transcription factors with DNA sequence motifs in gene promoters. While a handful of these circadian DNA sequence motifs have been characterized, the discovery of novel motifs will help to understand the circadian regulation of behavior. To this end, we identified a dominant mis-sense mutation in the SCN transcription factor *Zfhx3*, termed short circuit (*Zfhx3*^{Sci}), which accelerates circadian locomotor rhythms in mice. ZFHX3 regulates transcription via predicted AT motifs in target genes and the mutant protein has a decreased ability to activate consensus AT motifs *in vitro*. Using RNA sequencing, we found minimal effects on core clock genes in *Zfhx3*$^{Sci/+}$ SCN, whereas the expression of neuropeptides critical for SCN intercellular signaling was significantly disturbed. Moreover, mutant ZFHX3 had a decreased ability to activate AT motifs in the promoters of these neuropeptide genes. Lentiviral transduction of SCN slices showed that the ZFHX3-mediated activation of AT motifs is circadian. Moreover, the amplitude and robustness of these oscillations were decreased in

Zfhx3$^{Sci/+}$ SCN slices. In conclusion, by cloning *Zfhx3*^{Sci} we have uncovered a new circadian transcriptional axis that determines the period and robustness of behavioral and SCN molecular rhythms.

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Talk: Daniel Nätt, Friday May 22, 14:00

Stress in five-year-old children cause whole-genome loss of DNA-methylation in endogenous retroviruses - the link to adult neuropsychiatric disorders

Daniel Nätt,[1] Ingela Johansson,[2] Tomas Faresjö,[3] Johnny Ludvigsson,[2] & Annika Thorsell[1]

Childhood stress is associated with an increased risk of adult neuropsychiatric disorders, such as major depression and addiction. Studies report of epigenetic changes in adults with experienced childhood stress, but to better understand how these mechanisms may generate vulnerability to disease, we studied stress in five-year-old children. By combining hair cortisol measurements (a well-documented biomarker for chronic stress) with whole genome DNA-methylation profiles from blood samples, we show that high cortisol associates with a genome-wide decrease in DNA-methylation targeted to ZNF263 transcription factor binding sites. This type of zinc finger protein has previously shown to play an important role in protecting the genome from endogenous retroviral reactivation. In line with this, methylation loss was localized to endogenous retroviruses, as well as genes important for neurodevelopment and calcium transport. Since large scale hypomethylation of endogenous retroviruses, and a deficient calcium transport, are commonly reported in many stress related diseases, as well as in aging, our results point to a novel mechanism in how susceptibility to these diseases may develop. More importantly, due to the large amount of neurodevelopmental genes epigenetically affected by high cortisol, our results suggest that epigenetic biomarkers for neuropsychiatric disorders may be found in human blood samples. We are therefore currently evaluating a number of animal models to studying the correlation of epigenetic marks between brain and blood. In particular, we are interested in behavioral models for depression, anxiety and addiction, and how these interact with early adversity and endogenous retroviral reactivation within genes important for neurodevelopment.

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Talk: Hee-Sup Shin, Friday May 22, 14:20

Preventing return of fear by extinction training coupled with alternating bilateral stimulation increases BDNF and inhibitory transmission in amygdala: A neural mechanism of the psychotherapy for posttraumatic stress disorder.

Sukchan Lee1, 2, Jinhee Back1, Taesup Cho1, Boyoung Lee1, Ko Keun Kim1, Sang Jeong Kim2, & Hee-Sup Shin1*

Eye movement desensitization and reprocessing (EMDR), a well-established psychotherapy regimen for post-traumatic stress disorders in humans, is based on dual stimulation: recalling traumatic memory together with alternating bilateral sensory stimulation (ABS). However, the neurobiological basis for the connection between the dual stimulation and fear extinction is unknown. Here, we found that the mediodorsal thalamic nucleus (MD)-amygdala circuit is critically involved in this process. Importantly the visual ABS-coupled extinction training prevented the return of auditory-conditioned fear memory, suggesting fear memory erasure. Single-unit recordings in freely moving mice revealed that during the visual ABS-coupled extinction training, MD neurons fire at a persistently higher rate compared to that during the regular extinction training with conditioned tone only. This observation is consistent with our previous finding that enhanced firing of MD neurons facilitates fear extinction in the mouse (Lee et al., *N. Neurosci. 2012*). Furthermore, the ABS-coupled extinction training induced an increase of brain-derived neurotrophic factor (BDNF), a crucial regulator of synaptic plasticity, and inhibitory neuro-transmission in the amygdala, findings consistent with the blocking of fear relapse. In contrast, the BDNF and the inhibition level was suppressed in the regular extinction group who showed a fear relapse. Thus, a thalamic integration of dual stimulation signals into inhibitory fear circuits in amygdala appears to prevent the return of fear memory, delineating a neural mechanism underlying EMDR.

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Talk: Cynthia Bulik, Friday May 22, 14:40

The Gut-Brain Axis in Acute Anorexia Nervosa: Associations Between Intestinal Microbiota and Psychopathology Measures

Susan C. Kleiman, BSFS[1], Hunna J. Watson, PhD[2,3,4,5], Emily C. Bulik-Sullivan[6], Eun Young Huh, MS[7], Lisa M. Tarantino, PhD[2], Cynthia M. Bulik, PhD[1,2,8], and Ian M. Carroll, PhD[7]

The intestinal microbiota modulates weight regulation and behavior, but its role in anorexia nervosa (AN) remains unknown. Comorbid anxiety and depression are common in AN, and both have been linked to intestinal dysbiosis. We hypothesized that specific taxa in the intestinal microbiota would be associated with psychopathology in AN. We characterized the composition and diversity of the intestinal microbiota in AN patients at inpatient admission (n=16). The first stool sample after intake was collected. Within 48 hours, participants completed the Beck Depression Inventory, Beck Anxiety Inventory, and Eating Disorder Examination-Questionnaire. Genomic DNA was isolated from stool samples, and bacterial composition was characterized by 454 pyrosequencing of the 16S rRNA gene. Sequencing results were processed by the Quantitative Insights Into Microbial Ecology pipeline. Associations between psychopathology measures and alpha and beta diversity and taxa abundance of bacterial groups were examined with the tau-b correlation coefficient. Greater depression and anxiety were significantly associated with reduced abundance of Lachnospira, Roseburia, and Ruminococcus species, which have been associated with IBS, IBD, and mouse models of inflammation. Greater depression was also negatively associated with number of observed taxa and the Chao Diversity index. Higher EDE-Q scores were significantly associated with reduced abundance of Anaerostipes and Faecalibacterium species. Results suggest that the acute phase of AN shares similarities with the microbiotas of individuals with intestinal diseases that are marked by inflammation. Future directions include mechanistic investigations of the gut-brain axis in animal models of AN and association of microbial measures with recovery.

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Talk: Lee Henry, Friday May 22, 15:30

Application of the INTACT system to the study of neuronal cell types.

Lee Henry[1]

The brain is a complex structure composed of myriad neuronal cell types that are the building blocks of the circuits that control behavior in all metazoan organisms. We are interested in the transcriptional networks that both maintain the identity of these neuronal cell types and provide the basis for the extraordinary degree of plasticity that can be seen in neurons that populate circuits involved in complex behaviors such as learning and memory formation. To study these regulatory networks we and others have developed a method called the isolation of nuclei tagged in a specific cell type (INTACT). From the brain of *D. melanogaster* we have generated cell-type specific gene expression profiles, which provide a molecular inventory of both a neuron's functional capabilities and the transcriptional regulatory factors that direct gene expression in the profiled cell type. Lastly, we have begun to analyze both activity-induced transcription in defined cell populations and the affect of social context on neuronal transcription. A preliminary assessment of this work will be presented.

1 The Janelia Research Campus of the Howard Hughes Medical Institute. USA.

Talk: Amanda Crocker, Friday May 22, 16:00

Transcriptome-Wide Analysis of Single Drosophila Mushroom Body Neurons Reveals Learning-Related Changes in Gene Expression.

Crocker, A [1,2], Murphy, C [2,3], and Murthy, M [1,2]

High Throughput Sequencing, specifically RNAseq, is revolutionizing our understanding of neuronal function and transcriptional regulation. Using this new unbiased method to probe neuronal function, we set out to characterize a set of 5 identifiable neurons in the olfactory pathway of the fruit fly and their pre-synaptic partners. These neurons are important for the behavioral expression of long-term olfactory memories. To this end, we developed a workflow for harvesting single neurons via patch pipettes, amplifying the transcriptome and profiling through next generation sequencing. Then using a novel single fly behavioral assay, asked if there are transcriptional changes in these neurons following the induction of long term memory. Interestingly, we find that specific classes of genes undergo transcriptional up-regulation following long-term memory formation, and we are currently validating these results. Overall this work demonstrates the power of single cell RNAseq to define specific cell types and discover novel genetic networks driving behavior, which may only act in a small subset of neurons.

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Talk: Benjamin J. Matthews, Friday May 22, 16:30

Genome engineering and oviposition behavior in the mosquito Aedes aegypti

Benjamin J. Matthews[1,2], Kathryn E. Kistler[1], and Leslie B. Vosshall[1,2]

The mosquito *Aedes aegypti* is the primary vector of dengue, chikungunya, and yellow fever viruses and, through serial blood-feeding on humans, is responsible for hundreds of millions of infections annually. Female mosquitoes obtain a blood meal from human hosts, and use this to develop a clutch of approximately 100 eggs. Trap-entering assays show that blood-fed females use volatile cues such as relative humidity as an attractive cue to guide them towards egg-laying, or oviposition, sites at a distance. Once they have localized a potential site, oviposition requires direct contact with a liquid substrate before egg-laying begins. Conversely, *Ae. aegypti* demonstrate avoid high-osmolarity substrates with a half-maximal concentration corresponding to ~12% seawater, demonstrating that contact chemosensation guides the search for appropriate oviposition substrates.

To understand the genetic basis of these behaviors, we have identified candidate genes through transcriptome profiling of sensory tissues and developed methods for site-directed mutagenesis using the CRISPR-Cas9 system. We have achieved efficient mutagenesis via insertion and deletion, large genomic deletions, or insertions of exogenous DNA sequences such as fluorescent reporters. The ease and efficiency of our optimized CRISPR-Cas9 approach has allowed us to generate stable and precise loss-of-function mutations in 8 candidate genes thus far and forms the basis for a genetic exploration of this behavior in *Ae. aegypti* as well as future investigations of the neural circuit and genetic basis of other mosquito behaviors.

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Talk: Mike Lodato, Friday May 22, 17:00

Mosaic Mutations Trace Developmental and Transcriptional Histories of Single Human Neurons

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From the first cleavage division of the fertilized egg, somatic cells accumulate genetic lesions, so that each tissue within an individual, is a mosaic of distinct genotypes. However, the genome-wide frequency and characteristics of somatic mosaicism in non-cancerous cells are not known. We analyzed somatic single-nucleotide variants (SNVs) from whole-genome sequence (WGS) of 24 single human cerebral cortical neurons from three normal individuals, and profiled hundreds of additional cells and other tissues by targeted genotyping to analyze the landscape of somatic SNVs in normal human brain. We identified thousands of somatic SNVs, many apparently unique to a single neuron, and others shared between multiple cells, strongly suggesting that they occurred in a common progenitor, allowing us to infer lineage relationships between these cells. These data allowed us to show that small areas of the cerebral cortex are highly polyclonal and not derived from single neural progenitor cells. Also, we found that somatic mutations reflect known mutational processes shedding light on factors which shape the somatic genome in the human brain. One signature observed in neuronal mutations was transcription-induced DNA damage, and as a result important regulators of neural development and function were found to be mutated in single neurons, suggesting somatic mutations in grossly normal individuals might play a subtle role determining human phenotypes. Thus, analysis of somatic mutations in normal human neurons allowed us in infer lineage relationships between neurons and illuminated mutagenic forces impacting the somatic genome.

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Poster Abstracts

Poster 1

Effects of advanced paternal age on trajectories of social behavior and motor development in offspring.

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A strong association between advanced paternal age (APA) at conception and offspring's sexually-dimorphic neurodevelopmental disorders (autism, schizophrenia) has been observed in a number of epidemiological studies. Given abnormalities in social behavior and motor deficits are characteristic of both of these disorders, we assessed these functions in male and female inbred mice (C57BL/6J) across postnatal development (N = 104) in relation to paternal age. Three groups of offspring of (i) young (8 weeks old fathers), (ii) old (40 week old fathers) and (iii) very old fathers (48 week old fathers) were tested through a battery of behavioral tasks. The tests assessed both early development and behavior in adulthood, focusing on motor and social domains. Majority of the tests run on adult offspring were also run on fathers, in order to eliminate paternal effects that were not related to the father's age at conception.

We found differences in early motor skills and social behavior in both male and female offspring of older breeders, with adulthood persistence of these effects in males only. We showed that the social deficits were not present in the fathers of these offspring, confirming a *de novo* origin of an altered social trajectory in the offspring generation. Our study is the first investigation of the effects of APA on the developmental trajectory of behavior in rodent offspring, providing evidence for a causal link between APA, age-related changes in the paternal sperm DNA and neurodevelopmental disorders in their offspring.

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Poster 2

Prolonged maternal separation affect corticosterone levels and social play behavior in adolescent male but not female Wistar rats

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Early-life experiences are an important factor influencing further development of the individual. Adverse experiences leads to exposure of early stress that can have detrimental effects on several physiological systems. Maternal separation (MS) is a rodent model used to study the effects of early-life experiences. In this study two separation conditions were used: daily 15- (MS15) and 360-minute (MS360) separation of the litter from the dam during the first three postnatal weeks. In early adolescence, male and female offspring were subjected to a stress reactivity test for analysis of corticosterone levels prior to and after stress. In addition, social play behavior was assessed during mid-adolescence. There was a clear difference between male and female offspring in both tests performed. In the stress reactivity test there was no difference between the female groups while MS360 males showed higher basal corticosterone level than the MS15 males and a smaller decrease in corticosterone in the recovery phase. The amount of pinning during social play was affected by rearing with MS360 males having a higher frequency than MS15 males, while there was no difference among the females. That males but not females are affected by prolonged MS have previously been shown in adult animals and here we show that the

same is true for adolescent animals. Altered corticosterone levels during adolescence might in adulthood lead to changes in stress reactivity; what impact the slight change in social play might have needs further investigation.

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Poster 3

Heritability of human-directed social behaviour in beagles

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Dogs have developed unique social skills through domestication and co-evolution with humans. They can attract human attention, e.g. dogs have the ability to seek assistance when faced with a problem task. The aims of this study were to examine within breed differences in human-directed contact seeking in laboratory beagles as well as estimating its genetic basis. To investigate this, 498 beagles, bred and kept under standardised conditions at a research kennel, were tested in an unsolvable problem task. Contact seeking behaviours recorded included both eye contact and physical interactions. Behavioural data was summarised in four principal components (test interactions, social interactions, eye contact and physical contact) through a principal component analysis. Females had significantly higher scores on social interactions and physical contact and age had an effect on eye contact scores. Narrow sense heritabilities (h^2) were estimated at 0.32 and 0.23 for the two largest components but were not significant for the smaller components. Within this dog population, the results show a sex dependent behavioural variation in human-directed social behaviours and that eye contact seeking increased with age and experience. Hence, heritability estimates indicate a significant genetic contribution to the behavioural differences found in human-directed social interactions, implying that there is a genetic basis to dogs' social skills. Also, these skills can be shaped and improved through experiences. These results provides the chance to further investigate the genetics affecting dogs' social skills that could also play an important role into research on human social disorders such as autism.

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Poster 4

The effect of tumor necrosis factor alpha deficiency on behavior and serotonergic system in mice

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Tumor necrosis factor alpha (TNF-α) is a pro-inflammotory cytokine exerting both homeostatic and pathophysiological roles in the central nervous system. Mice deficient in TNF-α are one of the models to study the mechanism of TNF-α action in CNS as well as the role it plays in neuropathology and cognitive function. Unfortunately not a lot of studies have been devoted to the effect of TNF deficiency on cognition and brain chemistry. In this study we decided to compare the wild-type (C57Bl/6, WT) and TNF knockout (KO) mice behavior, levels of serotonin and 5-hydroxyindoleacetic acid (5-HIAA), the expression of serotonin system key genes in the cortex, hippocampus and midbrain.

WT and KO mice did not differ in anxiety and locomotor activity in the open field and plus-maze. In the Morris water maze mice of both strains didn't differ in acquisition, but during retention WT mice spend more time in the target sector as compared with the opposed one, while the KO animals didn't show preference in sectors.

In the hippocampus and midbrain 5-HIAA levels were significantly higher in KO mice, although the 5-HIAA/serotonin ration was significantly higher only in the midbrain in KO mice. Interestingly, in the midbrain there was no difference in the level of monoamine oxidase-A gene expression, being the basic enzyme degradation of serotonin to 5-HIAA, while in the hippocampus MAO-A gene expression was significantly greater in knockout animals.

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Poster 5

The relationship between cognition and personality is task- and age-dependent in the red junglefowl

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Cognition is defined as the way individuals perceive, process, store and act on environmental stimuli. Variation in cognitive processes can therefore strongly influence individuals' lives. Nevertheless, individual variation in cognition is investigated only in a limited number of species, and why there is individual variation is not well understood. A recently advancing research field in biology is 'animal personality', focusing on causes and consequences of consistent individual behavioural responses. Despite the potential interactions between cognition and personality, the relationship between them is still poorly investigated. Here, we explored links between cognition and personality by exposing young and adult red junglefowl (*Gallus gallus*) to a series of learning tasks and personality assays. The learning speed of individuals across tasks did not correlate, suggesting that there is no overall more 'intelligent' type. Variation in learning speed in simpler tasks was not influenced by personality. On the other hand, learning speed in a complex cognitive task was linked to exploration, but in opposite directions for juveniles and adult females. Explorative chicks learned faster than less explorative chicks, while for adult females, less explorative individuals were the faster learners. Our results demonstrate that individual variation in cognition can be related to personality where particularly variation in exploration is linked to variation in learning. Further, these results demonstrate that the relationship is task-dependent and can change over time. Our results therefore encourage further exploration of causality and investigation of the mechanisms underlying this relationship.

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Poster 6

Gene-environment interaction of gene expression in a mouse model of anxiety

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Anxiety disorders are complex diseases influenced by genetic and environmental factors, such as psychosocial stress. Little is known about the gene-environment interactions (GxE) in anxiety. We used chronic social defeat paradigm to induce anxiety-like behavior in two inbred mouse strains, C57BL/6 and DBA/2. Based on the social preference test conducted after social defeat, we divided the mice into stress susceptible and resilient groups. 61.5 % of C57BL/6 and 11.8 % of DBA/2 mice were resilient to stress. To investigate how genetic background affects the transcriptomic response to stress, we carried out RNA-seq in ventral hippocampus, a brain region regulating some aspects of anxiety-like behavior. We identified 407 genes with significant GxE (FDR < 0.01). To identify molecular pathways affected by stress, we carried out pathway analysis separately in each strain with the subset of genes having significant GxE and that were also differentially expressed between susceptible and resilient mice. The most significantly overrepresented pathways were Glioblastoma Multiforme Signaling, RhoGDI Signaling, Cell Cycle: G1/S Checkpoint Regulation, mTOR Signaling, and Signaling by Rho Family GTPases in C57BL/6J, and Ephrin B Signaling, Aryl Hydrocarbon Receptor Signaling, Breast Cancer Regulation by Stathmin1, Signaling by Rho Family GTPases, and Myc Mediated Apoptosis Signaling in DBA/2. Our results show that C57BL/6 and DBA/2 mice respond differently to social defeat stress both on the behavioral and brain transcriptome levels. C57BL/6 mice are innately less anxious than DBA/2 mice. Thus, the genetic background has an effect both on the innate behavior and on the response to environmental triggers.

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Poster 7

Molecular adaptation to social defeat stress: effects on prefrontal cortex transcriptome

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Chronic social defeat stress is highly validated mouse model of depression. We aimed to study dynamic changes

of genes expression during development of depression-like state in C57BL/6 mice. We analyzed the effects of social defeat stress of different durations (10 and 30 days) on prefrontal cortex transcriptome and depression-like behaviors. Mice exposed to 30-day stress (S30 group) showed high level of social avoidance, elevated immobility in the forced swim test, anhedonic behavior. Mice exposed to 10-day stress (S10 group) showed high level of social avoidance only. The analysis of RNA-seq data revealed significant differences in transcriptomic profiles between stressed and control mice at the both time points studied. We found that 473 and 35 genes were affected by stress in murine prefrontal cortex at 10th and 30th day, respectively. A few genes associated with depression (include *Grin2c*, *Daam2*) were in a unique list of transcripts differently regulated under chronic defeat stress (in S30 group). Special attention was paid to genes that were significantly altered in S10 group but resembled the control state after prolonged 30-day stress. The group included genes of extracellular matrix organization and cell adhesion, inflammatory response, tissue morphogenesis. Taken together our data suggest that a depression may be due to reduced response to stressful environmental factors at both the behavioral level and the level of gene expression.

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Poster 8

Behavioural differences and the heritability of behaviour in two selection lines of golden and Labrador retriever

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In dog breeding, selection is still ongoing and in some breeds a divergence has occurred through recent selection. Both golden retriever (GR) and Labrador retriever (LR) have two selection lines where one is bred for conformation and pet suitability (CT) and one for hunting traits (FT). We hypothesised similar behavioural differences between these selection lines and analysed data from the Dog Mentality Assessment, a standardized test battery. Also, we calculated the heritability for the behavioural traits. Behavioural data from 902 GR (698 CT and 204 FT) and 1672 LR (813 CT and 649 FT) was used. A principal component analysis revealed six components: fearlessness, play interest, chase proneness, social curiosity, social greeting and threat display. For five of the six components there were significant differences within each breed, but for only two the differences went in the same direction in both breeds. FT of both GR and LR showed higher play interest (GR: $F_{(1)} = 46.125$; $P < 0.001$; LR: $F_{(1)} = 29.420$; $P = 0.001$) and CT of both breeds showed higher threat display (GR: $F_{(1)} = 7.511$; $P = 0.006$; LR: $F_{(1)} = 18.640$; $P < 0.001$). The heritability was significant for all traits for both breeds and ranged from 0.13 for play interest in LR to 0.39 for threat display in GR. Thus, in spite of divergence due to selection for similar traits, FT of GR and LR generally behaved differently. Further research is needed on the underlying behavioural traits targeted in selection in these breeds.

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Poster 9

Effect of glial cell line-derived neurotrophic factor on depressive-like behavior, spatial learning and key genes of the brain dopamine system in genetically predisposed to behavioral disorders mouse strains

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The effect of glial cell line-derived neurotrophic factor (GDNF) on behavior and brain dopamine system in predisposed to depressive-like behavior ASC (Antidepressant Sensitive Cataleptics) mice in comparison with parental "nondepressive" CBA mice was studied. In seven days after administration (800 ng, i.c.v.) GDNF decreased escape latency time and the path traveled to reach hidden platform in Morris water maze in ASC mice. GDNF enhanced depressive-like traits in both "nondepressive" CBA and "depressive" ASC mice. In CBA mice, GDNF decreased functional response to agonists of D1 (Chloro-APB hydrobromide) and D2 (Sumanirole maleate) receptors, reduced D2 receptor gene expression in the substantia nigra and increased monoamine

oxydase A (MAO A) gene expression in the striatum. GDNF increased D1 and D2 receptor genes expression in the nucleus accumbens of ASC mice but failed to alter expression of catechol-O-methyltransferase, dopamine transporter, MAO B and tyrosine hydroxylase genes in both investigated mouse strains. Thus, GDNF produced long-term genotype-dependent effect on behavior and the brain dopamine system. GDNF pretreatment 1) reduced D1 and D2 receptors functional responses and D2 receptor gene expression in s. nigra of CBA mice; 2) increased D1 and D2 receptor genes expression in n. accumbens of ASC mice and 3) improved spatial learning in ASC mice. GDNF enhanced depressive-like behavior both in CBA and ASC mice. The data suggest that genetically defined variance in the cross-talk between GDNF and brain dopamine system contributes to the variability of GDNF-induced responses.

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Poster 10

Effect of chronic activation of 5-HT$_7$ receptors on behavior, 5-HT$_7$ and 5-HT$_{1A}$ receptors functional activity, and expression of key genes of the brain serotonin system

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Serotonin is a major neurotransmitter in both peripheral and central nervous systems. The wide variety of physiological and behavioral responses to serotonin is due to multiple 5-HT receptors. There is a lack of data on the interaction of 5-HT$_7$ receptors with other 5-HT receptor subtypes. Here we investigated the effect of chronic 5-HT$_7$ receptor activation on behavior, 5-HT$_7$ and 5-HT$_{1A}$ receptors functional activity, and expression of key genes of the brain serotonin system. It was found that chronic 5-HT$_7$ receptor selective agonist LP44 treatment produced considerable desensitization of 5-HT$_7$ receptors. 5-HT$_7$ receptor-mediated hypothermic response was three-fold lower in LP44-treated mice compared to control. Interestingly, chronic 5-HT$_7$ receptor activation produced significant desensitization of 5-HT$_{1A}$ receptors. 5-HT$_{1A}$ receptor-mediated hypothermic response was considerably lower in LP44-treated mice compared to control mice. At the same time, chronic LP44 treatment failed to alter 5-ht$_7$ and 5-ht$_{1A}$ genes expression in all investigated brain structures. However, 5-HT$_{1A}$ receptor protein level was significantly reduced in the midbrain and frontal cortex but not in the hippocampus of LP44-treated mice. It is necessary to note, that chronic LP44 treatment failed to alter behavior in tail suspension and open field tests, and test for catalepsy. The obtained data provide new evidence of the cross-talk between 5-HT$_7$ and 5-HT$_{1A}$ receptors.

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Poster 11

Voluntary exercise rescues behavioral deficits induced by neonatal alcohol exposure and increases adult hippocampal neurogenesis in mice

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Developmental alcohol exposure can produce a wide range of deficits collectively known as Fetal Alcohol Spectrum Disorders (FASD). FASD-related impairments in cognition and learning persist into adulthood and are accompanied by structural changes in the hippocampus. In rodent FASD models, neonatal alcohol exposure reduces the survival of adult born hippocampal neurons and impairs hippocampal-dependent behavior. Running increases adult neurogenesis levels and enhances behavioral performance. This study utilized two different models of third trimester alcohol exposure: saline or 20% ethanol solution (5g/kg split into two doses, two hours apart) on 1) postnatal day (PD)7 (Experiment 1) or on 2) PD5, 7 and 9 (Experiments 2, 3). In Experiments 1 and 2, animals received a running or sedentary intervention from PD35-PD80. To label dividing cells, *i.p.* injections of 50 mg/kg bromodeoxyuridine (BrdU) occurred from PD36-PD45. Behavioral testing happened between PD72-79. In Experiment 3, animals received BrdU on PD22-24. Behavioral testing occurred on PD51-56. Neither alcohol paradigm influenced the number of surviving BrdU+ cells in adulthood. Running significantly increased the number of BrdU+ cells across postnatal treatments. Behavioral results on the Passive Avoidance and the Y-Maze task indicate a PD5, 7 and 9, but not a PD7 alone, neonatal alcohol exposure impairs behavioral performance. Running rescued alcohol-induced behavioral deficits. These data suggest impaired behavioral performance is not due to neurogenesis deficits, but increased neurogenesis from exercise could still be related to the recovery.

Further, they illustrate the long-term influence of neonatal alcohol exposure and the beneficial impact of running on the alcohol-exposed brain.

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Poster 12

Dissecting Parent-of-origin Effects in Attachment, Anxiety, Social Behaviour and Vocalizations: a Longitudinal Investigation in Mice

Glenda Lassi, Valter Tucci

Mice accomplish full maturation after birth. We have studied epigenetic parental effects on a series of developmental and adult behaviours in mice. When separated from the dam, pups emit ultrasonic vocalizations (USVs) in their first postnatal days (PN) to restore closeness with the mother. The bond between the dam and the offspring, namely attachment, has not been assessed in mice before.

We have employed a diallel experimental design by using two inbred strains, BALB/c and C57Bl/6N, and their reciprocal hybrids. The parental strains differ for maternal care and anxiety. Each litter was either reared by the biological mother or by a CD1 foster mother.

In this study we recorded USVs at PN2-4-7-9-11; attachment was assessed at P18 in a novel adaptation of the Strange Situation Test (SST) and the anxiety-like behavior, tested with an Open Field, was measured both as pups and adults. Social habituation was tested at PN56.

As for the USVs emitted by pups, BALB/c background prevailed, especially in fostering. The behaviours measured in the SST are the reunion with the mother and the exploration of the stranger. Both revealed a paternally driven effect in fostered pups. BALB/c and C57Bl/6Nx BALB/c pups showed a partial maternal reunion interest and mother's presence did not affect their exploration of the stranger. In adulthood, their habituation to a stranger was faster. Anxiety levels revealed an opposite parent-of-origin effect in pups.

We report parent-of-origin differences in attachment and anxiety whilst a genetic effect accounts for USVs differences.

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Poster 13

Species-specific behavioral types are associated with microhabitat differentiation in Malawi African cichlid fishes

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The adaptive radiation of East African cichlid fishes has resulted in a species-rich flock that displays astounding trophic, morphological, and nuptial diversity. Within genera, fine-scale niche partitioning has resulted in sympatric sister species that inhabit definable microhabitats with distinct selection pressures. To date, work examining behavioral differences between sister cichlid species has focused almost exclusively on male-male competition and female mate choice, limiting our understanding of behavioral divergence to that of characters related to territory defense and sexual selection. However, more general behavioral adaptation to local environment likely plays an equally important role in shaping species-specific behaviors; African cichlid fishes are an ideal model with which to investigate whether behavioral syndromes develop during niche specialization, and identify the genetic basis of these species-specific, adaptive behaviors. To investigate behavioral divergence occurring during microhabitat differentiation, we tested sister species of Malawi cichlids found in either the sediment-free, rocky reefs or the sand-rock interface for a variety of environment-usage phenotypes in a controlled laboratory setting. Computer-aided analysis of home-tank grooming behavior and fish response to new objects and environments reveals distinct behavioral patterns between rock and interface species. We are now exploring the genetic basis of these traits using an interspecies hybrid cross, with genome-wide markers genotyped through double digest restriction site-associated DNA sequencing for linkage mapping studies.

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Poster 14

Genome engineering and oviposition behavior in the mosquito *Aedes aegypti*

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The mosquito *Aedes aegypti* is the primary vector of dengue, chikungunya, and yellow fever viruses and, through serial blood-feeding on humans, is responsible for hundreds of millions of infections annually. Female mosquitoes obtain a blood meal from human hosts, and use this to develop a clutch of approximately 100 eggs. Trap-entering assays show that blood-fed females use volatile cues such as relative humidity as an attractive cue to guide them towards egg-laying, or oviposition, sites at a distance. Once they have localized a potential site, oviposition requires direct contact with a liquid substrate before egg-laying begins. Conversely, *Ae. aegypti* demonstrate avoid high-osmolarity substrates with a half-maximal concentration corresponding to ~12% seawater, demonstrating that contact chemosensation guides the search for appropriate oviposition substrates.

To understand the genetic basis of these behaviors, we have identified candidate genes through transcriptome profiling of sensory tissues and developed methods for site-directed mutagenesis using the CRISPR-Cas9 system. We have achieved efficient mutagenesis via insertion and deletion, large genomic deletions, or insertions of exogenous DNA sequences such as fluorescent reporters. The ease and efficiency of our optimized CRISPR-Cas9 approach has allowed us to generate stable and precise loss-of-function mutations in 8 candidate genes thus far and forms the basis for a genetic exploration of this behavior in *Ae. aegypti* as well as future investigations of the neural circuit and genetic basis of other mosquito behaviors.

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Poster 15

Selective breeding for home cage hyperactivity produces hyperactive-impulsive behavioral deficits which are ameliorated by therapeutic amphetamine

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Attention deficit-hyperactivity disorder (ADHD) is a common behavioral disorder that is highly heritable (broad sense heritability estimates are approximately 75%). However, the specific genes and neurobiological risk factors remain a mystery, partly due to the paucity of good animal models. The goal of this study was to evaluate a line of mice selectively bred for increased locomotor activity in their home cages for face and predictive validity as an animal model for ADHD. One line (High-Active) was subjected to within family selection each generation for increased total distance traveled in the home cage on days 5 and 6 of a six day test. Video tracking precisely measured horizontal distance traveled continuously in the home cage. The other line (Control) was randomly bred each generation, avoiding sibling mating. The purpose of the first experiment was to test face validity of the model by determining whether High-Active mice also display motor impulsivity using the operant Go/No-go task as compared to Controls. The purpose of the second experiment was to test predictive validity of the model by determining whether administration of low, therapeutic doses of d-amphetamine ameliorates the motor impulsivity of the High-Active mice relative to Controls. Results from these studies indicate that the High-Active line of mice demonstrate increased measures of impulsive motor behavior in the Go/No-go task, which is paradoxically ameliorated by administration of d-amphetamine. These results support the High-Active line as a useful model for exploring the etiology of hyperactivity-associated comorbid behavioral disorders.

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Poster 16

Like father, like son: Do old male fowl show less aggression towards son's mating opportunities?

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Kin selection predicts that individuals will favour their relatives if this increases their inclusive fitness. Since older individuals have overall deteriorated reproductive ability (i.e. they senesce), we predict that older individuals will

benefit more than younger ones by promoting the reproductive success of their relatives. A suitable model for studies on the influence of age on responses to kin is the domestic fowl, *Gallus gallus domesticus*. In this species males form social hierarchies and dominant males commonly interrupt subdominant males' copulation attempts. Males also show reproductive senescence. We therefore investigate the differential behaviour of dominant male domestic fowl towards related and unrelated subordinate males during mating. We demonstrate that older males were less likely to interrupt subdominant males' copulations than young males. Further, dominant males were overall less likely to interrupt related subdominant males' copulations than unrelated subdominant males' copulations, thus favour kin over unrelated males. However, when we compared old and young dominant males, old males did not seem to favour their relatives any more strongly than young males. This suggests that old male fowl do not compensate for their senescing reproductive success by being more accepting towards younger relatives, but that the effect we observe is due to an overall bias in favour of kin by all males. Our study demonstrates kin selection in the fowl, presents a novel approach to the likely role of age in social interaction, and encourages further studies to consider the effect of senescence on kin selection.

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Poster 17

8-OH-DPAT and thermoregulation in 5-HT_{1A}-receptor mutant mice.

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The serotonin 1A (5-HT_{1A}) -receptor is involved in a wide range of physiological functions such as in the regulation of body temperature. Studies have shown that in mice, the hypothermic response induced by the full agonist at the 5-HT_{1A}-receptor 8-OH-DPAT is mediated by presynaptic 5-HT_{1A}-receptors. In contrast, investigations in humans and rats detected an involvement of postsynaptic 5-HT_{1A}-receptor. In our study we used a transgenic mouse line with a permanent overexpression of the 5-HT_{1A}-receptor in the projection areas of serotonergic neurons. We investigated the basal body temperature and the hypothermic effect of different dosages of 8-OH-DPAT (0.1mg/kg – 4 mg/kg ip.) in male transgenic mice in comparison to NMRI wild-type males using radio telemetry, a method that allows non-invasive recordings of body temperature. The basal body temperature of transgenic mice was lower than in NMRI wild-type mice (transgenic mice: 36.0 °C; NMRI wild-type mice: 37.4°C). In both genotypes, hypothermia by systemic administration of 8-OH-DPAT was induced in a dose dependent manner. However, the temperature decrease was more pronounced in transgenic mice with -2.8 °C compared to -1.5 °C in NMRI wild-types. Dose response curves of 8-OH-DPAT revealed an ED50 = 0.4 mg/kg in transgenic and ED50 = 0.57 mg/kg in NMRI wild-type mice. Our results suggest that the postsynaptic 5-HT_{1A}-receptor is involved in the regulation of body temperature in mice.

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Poster 18

Oxytocin and vasopressin genes in children's externalizing psychopathology: a cognitive endophenotype approach

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Externalizing problems – operationally defined as conduct and attention/hyperactivity difficulties – are among the most common mental health problems of children. Research suggests that these problems are best considered along a continuum that varies genetically throughout the population. Despite this, little is known about the discrete genes that influence behavioral problems, or the mechanisms through which they operate. The current study examined a genotype-endophenotype- phenotype model of externalizing psychopathology in 320 preschool-aged children. Markers of the oxytocin (OXT) and arginine vasopressin (AVP) genes were selected as candidates owing to their known association with human cognition and behavior. We then tested whether two cognitive endophenotypes – theory of mind (ToM) and executive functioning (EF) – mediated the effect of OXT and AVP on externalizing psychopathology. Conduct and attention/hyperactivity problems were assessed at age 4.5 using a previously validated rating scale. ToM and EF were measured using age-appropriate standardized and/or observational tasks. Using a family-based association design and controlling for non-genomic confounds (age, gender, socioeconomic status), support was found for an association between OXT markers rs2740210 ($p = .0077$) and rs2770378 ($p = .022$), and AVP marker rs3761249 ($p = .022$), and externalizing problems.

Further, ToM and EF were shown to independently and jointly predict externalizing problems, and the association between each marker and externalizing problems was reduced in magnitude after adding these variables to the genetic model. These results suggest that genetic variation in OXT and AVP may contribute to individual differences in externalizing problems, and these effects may partially operate through children's emerging neurocognitive abilities.

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Poster 19

Epistasis and the Genetic Architecture of Drosophila Aggressive Behavior

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Most animals display aggressive behavior to secure food resources, protect against predators and facilitate access to mating partners. Inappropriate or excessive aggression has detrimental consequences for an individual, which can lead to lower fitness. Aggressive behavior is genetically complex, influenced by many genes as well as interactions with the environment. However, the genetic pathways affecting variation in aggressive behavior are evolutionarily conserved, enabling general inferences to be drawn from genetic analysis using model systems. We investigated the natural genetic variation of aggression using the Drosophila melanogaster Genetic Reference Panel (DGRP), a collection of 205 inbred lines with fully sequenced genomes. We performed a genome wide association study (GWAS) and identified variants associated with variation in aggression. Additionally, we performed an independent experiment to replicate causal candidate variants by creating an advanced intercross population (AIP) from 6 lines representing the extremes of the DGRP and performed extreme quantitative trait loci (xQTL) mapping for aggressive behavior. We observed that alleles significantly associated with aggression in the AIP replicated the allelic effect on aggression from the 6 extreme DGRP lines. Additionally, we generated a network of epistatic interactions using a model that tests for pairwise marker interactions across the DGRP. This analysis revealed that genes from these two populations are highly interconnected at the network level even though there is very little overlap of genes from the GWAS in the DGRP and AIP. Finally, we used single homozygous and double heterozygous mutants to experimentally validate computationally predicted epistatic effects generated by this network.

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Poster 20

The search for stress-sensitive time early periods in the precocial chicken

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The postnatal developmental period is sensitive for vertebrate species, and stressful environmental stimuli could have long-lasting effects on the organism's behaviour and stress response. Precocial birds such as the chicken show a reduction in HPA-axis responsiveness if stressed during the first two weeks of life, effects that also lead to transgenerationally observable changes. In our experiment three critical windows of time were chosen and three groups of chicks were each exposed to one full week of mild stress exposure by social isolation and restraint at one, eight or 17 weeks of age. Offspring from within each group were raised until sexual maturation, and hypothalamus-enriched tissue from animals in both generations were used for the subsequent genetic analysis after culling.

Microarray data of RNA indicated no significant changes in gene expression between groups and the control among the thousand most differentially expressed (DE) genes. Neither could any significant effects be seen transgenerationally when looking for correlational changes in the overlap of the thousand most DE genes. Correlation plots do however indicate a positive trend for the overlap, but R-square tell us that the fit is less than required.

Gene ontology (GO) analysis of the most DE genes however identified a few GO terms of relevance to the stressful treatment, amongst them terms like neurotransmitter transporter activity, immune system processes,

behaviour and hormone activity. Genes within these terms are such as *AVPR2*, *OXT*, *PMCH* and *SLC6A4*, a serotonin transporter.

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Poster 21

Uppsala University Behavioral Facility (UUBF) – for the study of mouse, rat and fish behavior.

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Uppsala University Behavioral Facility (UUBF) is a non-profit core facility that is supported by the Faculty of Medicine and Pharmacy, Uppsala University. The aim is to provide services regarding administration and organization of behavioral tests for research groups at Uppsala University, as well as external groups. We can offer a large array of behavioral tasks for mice, rats and fish.

At the facility we can provide equipment and protocols for behavioral experiments. Several explorative-based tests and tests for motor behavior, learning and memory tests, sensorimotor tests and cognitive tests can be run. We can also help you with data analysis and interpretation, writing ethical applications and training and guidance in experimental design and help with statistical analyses. At UUBF we provide the use of specific data analysis programs for studies of behavioral recordings and advanced statistical analysis, including non-parametric and parametric statistics and principal component analysis. Welcome to contact UUBF for discussing the details of planning and conducting your behavior experiments.

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Poster 22

Born to run: The neural transcriptome signature of mice selectively bred for high voluntary wheel running

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Exercise is important for an organism's health and wellbeing. The motivation to exercise varies according to an individual's genetics and physiology. We used a rodent model consisting of four mouse strains selectively bred for high voluntary wheel running and four randomly bred control mouse strains to uncover the molecular underpinnings of increased motivation for exercise. The striatum was dissected and RNA was extracted and sequenced from four individuals of each line. We found multiple genes and gene systems with strong relationships to both selection and running history. Among these genes were the serotonin receptor subunit *Htr1b* subunit and the marker for both glutamatergic and GABAergic signaling *Slc38a2*. Systems analysis of the raw results found enrichment of tyrosine kinase related genes. We explored alternative splicing, finding a splice variant affecting the Golgi signaling domain in the Wnt signaling gene *Tmed5*. Using weighted gene coexpression network analysis, we found a cluster of interrelated coexpression modules with relationships to running behavior. From these coexpression modules, we built a coexpression network correlated with running that predicts a mechanistic relationship between transcriptional regulation by nucleosome structure, a system implicated in our previous work, and *Htr1b* expression, implicated in the current work. Using the Library of Integrated Cellular Signals, we found a number of small molecules predicted to act both agonistically and antagonistically to motivation to exercise. Altogether, these findings support a neurobiological framework where motivation, mediated by dopamine, is modulated both by the primary neurotransmitters glutamate and GABA and by neuromodulators in response to nucleosome structure.

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Poster 23

Adult neurogenesis modulates novelty exploration

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The extent to which adult born neurons in the dentate gyrus are involved and necessary for cognitive and affective behaviour remains controversial. This is largely due to the difficulty in evaluating whether behavioural differences are mediated by or merely correlate with adult neurogenesis. More refined experimental and statistical designs can improve our understanding of the adult neurogenesis-behaviour relationship. To this end, we present a high power unbiased assessment of the relationship between a large number of behavioural variables and the neurogenesis markers doublecortin and Ki67 in mice of two strains at two ages. Using several steps to eliminate false positive results, the majority of behavioural variables show no association with neurogenesis. Notable exceptions are variables measuring different aspects of exploration measured during the time the animals were introduced into the IntelliCage. On these variables adult neurogenesis has a modulating effect, resulting in slower exploration of a novel environment with higher neurogenesis.

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Poster 24

Dopamine Bi-directionally Regulates Alcohol Memory Valence

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Reward neural circuitry must accurately encode the affective outcome of an organism's experiences to successfully guide future behavior. The dynamic reconstructive nature of memories, however, makes these affective valences highly susceptible. Dysregulation of reward circuitry is thought to underlie many maladaptive and pathological behaviors including those attributed to addiction. Intriguingly drugs of abuse, such as alcohol, have both aversive and rewarding properties; however, the abiding memories of an intoxication experience are for the rewarding properties. Similarly, in the common fruit fly, *Drosophila melanogaster*, aversive alcohol memories are short-lived, whereas the rewarding alcohol memories are enduring [1]. A compact genome, small but sophisticated brain, impressive array of neurogenetic tools and robust motivated response for alcohol make *Drosophila* an ideal model for studying the neuronal circuitry mechanisms underlying aversive and rewarding alcohol memories. Alcohol memories in *Drosophila* require an associative central brain structure called the mushroom bodies (MB) and its dopaminergic innervations. Interestingly, MB dopaminergic axons terminate in discrete compartments that tile the MB axonal lobes. Using a set of highly specific split-GAL4 dopaminergic driver lines [2], we have identified a simple circuit that is required for the switch between aversive and appetitive memory expression [3 and subsequent work]. We describe how dopaminergic modulation of the mushroom body mediates the switch from aversive to appetitive memory for alcohol intoxication. This work provides valuable insight to the dynamic qualities of memory and how the long lasting reward memories for alcohol intoxication are formed.

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Poster 25

Intergenerational consequences of fetal programing by in utero exposure to ethanol in rats

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Background: The consequences of prenatal ethanol (PE) exposure vary in their severity. Intergenerational effects might contribute to this variation, and the purpose of this study is to identify whether grandmaternal ethanol exposure impaired hippocampus-dependent learning and memory in the second-generation progeny and if it does, would the transfer occur via altered hippocampal DNA methylation of insulin pathway genes.

Methods: Sprague-Dawley (S) dams received a 5% ethanol liquid diet and one of the two control diets (*ad libitum* chow, or an isocaloric liquid diet pair-fed to the ethanol dams). Their offspring, the first generation progeny (SS F1), were mated with naïve Brown Norway (B) males and females to generate the second generation SB F2 and BS F2 descendants. Hippocampus-dependent contextual fear memory, anxiety and activity levels were assessed in adult F1 and F2 animals using the fear conditioning (FC) and open field tests (OFT). DNA methylation of selected CpG islands in the insulin receptor (*Insr*), insulin-like growth factor 2 receptor (*Igf2r*) and growth factor receptor-bound protein 10 (*Grb10*) genes in the hippocampus were measured across the generations.

Results: Both SS F1 male and female offspring exposed to PE exhibited deficits in fear memory, but only the PE-exposed SS F1 females transmitted this deficit to their SB F2 progeny. Hippocampal DNA methylation profiles of *Insr*, *Igf2r*, and *Grb10* showed matrilineal transmission as well.

Conclusions: Grandmaternal ethanol consumption affects hippocampus-dependent fear memory and DNA methylation of insulin pathway genes known to affect cognition via matrilineal transfer.

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Poster 26

Genome-wide association for prepulse inhibition in mice implicates hippocampal expression QTL for Ambra1

Laura J. Sittig[1], Peter Carbonetto[1], Kyle Engel[1], Kate Krauss[1], and Abraham A. Palmer[1]

Prepulse inhibition (PPI), a measure of sensorimotor gating, is disrupted in a number of psychiatric disorders including schizophrenia. Laboratory measures of PPI in inbred mice demonstrate that PPI is highly heritable. Here we studied PPI in a panel of 30 common inbred mouse strains. Female mice from each of the 30 inbred strains were crossed with inbred C57BL/6J males, creating a panel of F1 mice. We examined PPI in this cohort and subsequently created an independent replication of this cohort, resulting in a combined sample of ~20 F1 mice/strain (>600 total mice). Genome-wide genotype data for F1 mice were obtained from existing databases and used to perform genome-wide association. Mega-analysis of the two study cohorts both identified a ~1 Mb locus on Chromosome 2 containing a cluster of olfactory receptor genes, which we believed were unlikely to account for the association with PPI. Therefore, we searched for expression QTL (eQTL) that map to the same interval. Expression array data available from the Hippocampus Consortium M430v2 RMA dataset (genenetwork.org) indicate that this locus overlaps a cis-eQTL for hippocampal *Ambra1* expression levels (LRS=19.5). *Ambra1* expression levels were correlated with PPI phenotype for strains present in both datasets. *Ambra1* has been associated with schizophrenia in European case-controls, suggesting that our results may be convergent with the results of human genetics studies. Here we show the association of an expression-QTL for *Ambra1* with PPI in mice, suggesting a putative neurobiological basis for its association with schizophrenia in humans.

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Poster 27

The role of chromatin remodelling factor CHD7 in cerebellar development and autism in a conditional mouse line

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ASD are a group of neurodevelopmental disorders with early onset, characterized by deficits in two core symptoms (social and communicative deficits and stereotyped behaviours). While the etiology of autism is still unknown, the strongest evidence appears to be genetic. Haploinsufficiency for the gene encoding chromatin remodelling factor CHD7 is the major cause of CHARGE syndrome, a condition associated with autism-like behaviours. CHD7 is expressed in the population of proliferative granule cell progenitors (GCps) that drives postnatal growth and foliation of the cerebellum. Loss of CHD7 from GCps reduced proliferation and enhanced neuronal differentiation, resulting in cerebellar hypoplasia. As neuroanatomical defects affecting the cerebellum are observed in autistic patients, we have generated a conditional mouse line (Chd7 deletion in GCps from E12.5 using Math1Cre) with hypoplasia of the lobules VI-VII, which allows us to determine the behavioural consequences of cerebellar defects. In order to evaluate the precise onset of vocal and motor alterations, we have analysed ultrasonic vocalizations (USVs) and spontaneous motor behaviours during the first two postnatal

weeks in the Chd7 mutant line. Furthermore, we have assessed the presence of communicative, social and motor deficits, repetitive and anxiety-like behaviours, as well as cognitive ability and flexibility at adulthood. Preliminary data show motor and coordination difficulties in Chd7 mutant pups and adult mice, in line with motor alterations seen in ASD patients. Social and repetitive behaviours appear unaffected, indicating that cerebellar hypoplasia per se is not sufficient to cause abnormalities in these behaviours.

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Poster 28

A Vglut2/Pitx2 subpopulation of the subthalamic nucleus is important for regulation of locomotion and reward processing

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(* equal contribution)

The subthalamic nucleus (STN) is an important area of the basal ganglia, anatomically arranged in a key position to modulate all types of motor-actions linked to higher brain functions. Its important role in locomotion has been shown by the successful use of high-frequency stimulation (HFS) of the STN as treatment for Parkinson's disease, however the mechanisms by which HFS modulate STN activity is unknown. In order to increase the current understanding of the glutamatergic nature of the STN, we characterized the expression of Vesicular Glutamate Transporters (VGLUTs 1-3) in the mouse STN and confirmed that Vglut2 is the predominant subtype. More importantly we were able to identify a subpopuplation of the STN, characterized by co-expression of Vglut2 and the paired-like homeodomain2 (Pitx2). Conditional knockout (cKO) of this subpopulation resulted in a decrease of Vglut2 expression by 40% as well as with a substantial but restricted reduction of glutamate transmission. The cKO mice displayed hyperlocomotion and decreased latency in the initiation of movement, while preserving normal gait and balance. Altered DAT levels in combination with slower DA clearance most likely indicate elevated extracellular striatal DA levels that drive the hyperactive phenotype (Schweizer *et al*. 2014). A more recent analysis looking at reward processing has also shown that the Pitx2cre/Vglu2 cKO mice display decreased sucrose consumption in an operant self-administration setup, a finding likely coupled to a reduction of dopamine release in the ventral striatum. Cognitive and affective abilities such as spatial cognition, social function and level of impulsive choice remained undisturbed in the cKO mice. Our results demonstrate that limiting, but not eliminating, the expression of VGLUT2 in the STN is sufficient to achieve results similar to STN high frequency stimulation but without unwanted cognitive side-effects. Finally, our findings suggest that the Pitx2/Vglut2 co-expressing subpopulation of the STN is involved in regulation of dopamine transmission from the nucleus accumbens and in reward related-behaviours.

Poster 29

Genetical genomics of fearful behaviours under chicken domestication

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Domestication involves strong selection for behavioural traits. Domestic chickens differ from wild in fearful behaviours, stress response and social behaviour. This genetic divergence makes wild by domestic crosses powerful study systems for behaviour genetics. We perform quantitative trait locus mapping of behaviour and gene expression in an advanced intercross of wild Red Junglefowl and domestic White Leghorn chickens. We assay open field, social reinstatement and tonic immobility behaviour in 572 chickens. We also measure transcriptome-wide gene expression in the hypothalamus 129 individuals. These mapping studies reveal 40 loci for behaviour and hundreds of loci affecting gene expression. We combine these data to find candidate quantitative trait genes that may affect these behaviours by means of changes in gene expression. In particular, *STK17A* and *GABRB2* are candidates for open field behaviour, where we also find that they affect similar behavioural traits in *Drosophila melanogaster* RNA interference lines. We mine published human and mouse

mapping studies to find suggestive evidence of effects of some of these genes in human psychiatric disorders and in mouse strains. We also isolate candidates for tonic immobility and social reinstatement behaviour. *ACOT9* and *PRDX4* are candidates for both traits on chromosome 1. This locus coincides with a published tonic immobility locus in quail. This suggests, again, cross-species conformity of some of these behaviour genes. It also coincides with a published locus affecting muscle pH and meat quality in chickens. This may be due to pleiotropic effects on this production trait and fearful and social behaviour.

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Poster 30

Effects of Pharmacogenetic Manipulation of the Nucleus Accumbens on Neuronal Activity and Alcohol-Related Behaviors

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Chronic alcohol intake leads to long lasting changes in reward-related neuronal circuitry. The nucleus accumbens (NAc) is an integral component of this circuitry. We used a pharmacogenetic approach to alter NAc activity and measure alcohol-related behaviors in mice. We used the mutagenized muscarinic G protein-coupled receptors hM3Dq and hM4Di that are selectively activated by clozapine-N-oxide (CNO). We tested the ability of CNO to change NAc activity and assessed the effects of altered NAc activity on binge-like alcohol drinking, tastant intake, and alcohol reward.

C57BL/6J female mice were stereotaxically injected with AAV2 hSyn-HA hM3Dq, -hM4Di, or -eGFP bilaterally into NAc. Experiments were carried out to verify CNO induced changes in NAc activity (via ex-vivo whole cell electrophysiological recordings). We tested the effect of altering NAc activity on binge ethanol intake (and intake of sucrose, quinine, and water) using the drinking in the dark paradigm (n=9-10/group). We also evaluated the effects of altering NAc activity on the affective properties of ethanol using conditioned place preference (n=9-10/group).

CNO increased NAc firing in hM3Dq positive cells and decreased firing in hM4Di cells, confirming the ability of these channels to spatially and temporally alter neuronal activity. Increasing NAc activity significantly decreased binge drinking ($p<0.05$) without altering intake for other tastants. Preliminary data suggest that altering NAc activity is not rewarding and does not change the rewarding effects of ethanol. Ongoing experiments aim to identify the specific striatal sub-regions and cell-types important for reduced alcohol intake.

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Poster 31

Involvement of C1473G polymorphism in mouse Tph2 gene in chronic ethanol treatment effect on behavior, 5-HT1A, BDNF and TrkB genes expression in brain

DV Bazovkina[1], AS Tsybko[1], TV Ilchibaeva[1], AV Kulikov[2]

Tryptophan hydroxylase-2 (TPH2) is the rate limiting enzyme of serotonin (5-HT) synthesis in the brain. The 1473G allele of the mTPH2 C1473G polymorphism is associated with reduced enzyme activity and serotonin synthesis rate in brain as well with low forced swim immobility duration.

The aim was to evaluate involvement of the mTPH2 C1473G polymorphism in chronic ethanol treatment effect on behavior, brain expression of serotonin-related and BDNF-related genes in mice of congenic B6-1473C (C/C) and B6-1473G (G/G) lines created by 9 successive backcrossings of F1[CC57BR(G/G)xC57BL/6(C/C)] males with females of C57BL/6 strain. The influence of chronic ethanol treatment (1.6 g/kg, i.p.,14 days; control groups received saline) was estimated on 1) behavior in the open-field, forced swim tests; 2) expression of genes encoding 5-HT1A, 5-HT2A receptors, tryptophan hydroxylase-2, serotonin transporter, BDNF (Brain-derived neurotrophic factor) and BDNF receptor TrkB in the brain.

Chronic ethanol administration led to increased time spent in center of open-field ($p<0.001$) and augmented forced swim immobility ($p<0.05$) only in B6-1473G mice comparing with corresponding saline groups. 5-HT1A

gene expression was reduced in frontal cortex ($p<0.05$) and augmented in hippocampus ($p<0.05$) and 5-HT2A gene expression was increased in hippocampus ($p<0.05$) only in alcoholized B6-1473G animals. Moreover, in B6-1473G mice BDNF gene expression was increased in midbrain ($p<0.001$), reduced in frontal cortex ($p<0.05$) and TrkB gene expression was decreased in midbrain after chronic ethanol exposure.

Consequently, B6-1473G mice carrying 1473G allele of the mTPH2 C1473G polymorphism showed high sensitivity to effect of chronic ethanol treatment.

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Poster 32

Drug Repurposing for Tobacco Dependence Treatment

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Tobacco dependence is one of the most catastrophic health hazards to face the human population. One person dies from tobacco related disease every second worldwide, a situation compounded as the most efficacious treatment strategies achieve <50% success. Consequently, a need exists to identify new treatments.

We used complementary behavioral assays in zebrafish, locomotor activation and conditioned place preference (CPP), to identify modifiers of nicotine response. Sequential screening was used to identify candidate medications for repurposing as tobacco cessation treatment.

This study extends our initial pilot evaluation of 39 neural-target enriched medications, from which 8 candidates were identified using the larval locomotor activation assay. Here, we report on an additional 131 non-enriched but physician-vetted medications. Following toxicity testing, 62/131 were selected for nicotine response attenuation testing, with 23 showing significant response. Cinnamon oil stimulus control studies subsequently identified 1/23 as a candidate for follow-up evaluation.

In addition, pilot-study candidates were evaluated using CPP. Diazepam (3.5 μM), a benzodiazepine for anxiety disorders, significantly blocked the nicotine-conditioned response without impacting overall locomotion. Importantly, as nicotine and diazepam were co-administered, this effect can not be due to diazepam's anxiolytic effect preventing a nicotine anxiolytic effect, as this would be expected to enhance not reduce the conditions response.

Our results to date demonstrate that medications capable of attenuating the physiological response to nicotine can be rapidly identified through a larval zebrafish locomotor screen. Results of the CPP diazepam assay strengthen the evidence suggesting this medication should be evaluated in further human studies for treating tobacco dependence.

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Poster 33

Development of a mouse model of adolescent binge caffeinated alcohol consumption

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Adolescent binge consumption of caffeinated alcoholic beverages is a growing concern. Caffeine may mask alcohol's sedative effects, increasing risk for continued drinking despite significant intoxication. However, the available human data is equivocal. The goal of the current work was to adapt the Drinking-in-the-Dark paradigm to model adolescent binge consumption of a caffeinated alcohol solution. Adolescent and adult male C57BL/6J mice were provided daily 2hr access to alcohol (20% v/v), caffeine (0.03% w/v), or the combined solution for 14 days. Fluid access was extended to 4hrs on days 7 and 14, and concurrent home cage locomotion was assessed throughout. Adolescent and adult mice consumed physiologically relevant amounts of daily alcohol, caffeine, and the caffeinated alcohol solutions, and the added caffeine significantly increased binge alcohol consumption

for both adolescents ($p<0.001$) and adults ($p<0.05$) by day 14. Consumption of the caffeinated alcohol solution produced locomotor stimulation that was greater than that produced by consumption of caffeine alone in adolescent mice ($p<0.001$), and adolescent mice appeared to exhibit overall greater sensitivity to the locomotor stimulant effects of caffeinated alcohol than adult mice despite similar 2hr intakes. These results suggest that 1) repeated binge caffeinated alcohol consumption may lead to neuroadaptation resulting in increased alcohol intake, 2) adolescence is a time of greater vulnerability to such neuroadaptation, and 3) caffeine is a more potent driver of binge alcohol drinking and associated locomotion during adolescence. This new mouse model should inform as to how adolescent binge consumption of caffeinated alcoholic beverages uniquely alters brain and behavior.

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Poster 34

Is optimism affected by personality? A test of cognitive judgment bias in red junglefowl chicks

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Animal cognition and thus the way animals interpret their surroundings can include biases. Cognitive judgment bias is one type of cognitive bias. These biases can be positive or negative, resulting in more optimistic or pessimistic interpretation of stimuli. Such optimism or pessimism can be tested when observing responses to ambiguous cues intermediate of cues with known positive and negative values. We have recently demonstrated that individuals' responses to cognitive judgment bias tests are affected by environment during rearing. However, why individuals exposed to the same conditions differ in their cognitive judgment bias is not clear. Variation in personality (i.e. consistent individual differences in behaviour) has the potential to explain some of this variation due to the known impact personality can have on how individuals respond to their surroundings. Here, we therefore explored the extent to which personality of individuals explains their level of optimism. We trained red junglefowl chicks (*Gallus gallus*) to associate one colour cue with a reward, while another colour cue was unrewarded, before observing their reactions to a gradient of intermediate cues. The personality of individuals was scored by exposing chicks to novel arena - novel object - and tonic immobility tests. We show that less nervous individuals interpret ambiguous cues more positively and were therefore more optimistic. Nevertheless, the influence of personality was small. More research is therefore needed to further our understanding of why we observe variation in optimism specifically, and cognitive biases in general.

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Poster 35

Dual-trait Selection for Excessive Alcohol Drinking

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Alcohol abuse and dependence typically presents as abusive patterns of repeated intake. Such drinking characteristically involves binge-like patterns of drinking, which are defined by the NIH-NIAAA as a pattern leading to blood ethanol concentrations (BECs) > 0.8 mg/ml (i.e., exceeding the legal limit for driving) during a period of approximately 2 hr. In addition, most individuals diagnosed with an Alcohol Use Disorder also repeatedly drink large amounts chronically. Both chronic high-intake and binge-like drinking have been studied in genetic animal models. The cHAP mouse line was selectively bred for high levels of chronic intake during continuous access alcohol preference (AP) to both 10% alcohol and water, and cHAP mice drink as much as 25-30 g/kg/day. The High Drinking in the Dark replicate lines of mice (HDID-1 and HDID-2) were selected for reaching high BECs (approximate 1.5 mg/ml) after a 4 hr period of binge-like drinking. The drinking in the dark test, administered during the animals' circadian dark period, offers animals a single bottle of 20% alcohol. We review several lines of evidence suggesting that 2-bottle preference drinking and DID are largely distinct genetic traits. We recently created a new selected line – HAP-HDID mice – by intercrossing the cHAP and HDID mouse lines. We have bred on the basis of a dual-trait selection index that weights DID-BEC and AP equally. After 4 selected generations, the HAP-HDID line is showing increases in both AP and DID-BEC across generations. Our goal is a genetic animal model of risk for excessive, and sustained, alcohol drinking.

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Poster 36

Effect of microgravity on GDNF and CDNF genes expression in the mouse brain

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Mice were exposed to one month spaceflight on Russian biosatellite BION-M1 to determine its effect on the expression of genes involved in the maintenance of the mouse brain dopamine system. In the current paper we focused on the genes encoding glial cell-line derived neurotrophic factor (GDNF) and cerebral dopamine neurotrophic factor (CDNF). Spaceflight reduced expression of GDNF gene in the striatum and hypothalamus but increased it in the frontal cortex and raphe nucleus area. At the same time, actual spaceflight reduced expression of gene encoding CDNF in the substantia nigra but increased it in the raphe nucleus area. To separate the effects of spaceflight from environmental stress contribution we analyzed the expression of the investigated genes in mice housed for 1 month on Earth in the same shuttle cabins that were used for spaceflight, and in mice of the vivarium control group. Shuttle cabin housing failed to alter the expression of the GDNF and CDNF genes in investigated brain structures. Thus, actual long-term spaceflight produced dysregulation in genetic control of GDNF and CDNF genes. These changes may be related to down-regulation of the dopamine system after spaceflight, which we have shown earlier.

1 Department of Behavioral Neurogenomics, Institute of Cytology and Genetics SB RAS, Novosibirsk, Country Funding Support: Russian Scientific Foundation grant №14-25-00038, RUSSIAN FEDERATION.

Poster 37

Alteration of BDNF expression in genetically defined highly aggressive and nonaggressive rats.

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Brain-derived neurotrophic factor (BDNF) plays important role in neuronal survival, development, differentiation and plasticity. It is known that mice with decreased BDNF expression including knockout and conditional knockout showed increased intermale aggression. In our study we focused on BDNF expression in Norway rats selectively bred for more than 60 generations for high level of aggression forwards to man and its absence.

Considerable differences between the highly aggressive and the nonaggressive rats were shown both in BDNF mRNA level and protein level. A significantly increased BDNF mRNA level was found in the frontal cortex of aggressive rats compared to nonaggressive rats. BDNF mRNA levels in the midbrain and hippocampus were unaltered. At the same time, a significantly increased BDNF level as well as pro-BDNF level was found in the hippocampus of aggressive rats compared to nonaggressive rats. In the midbrain of aggressive rats increased pro-BDNF protein level was observed while BDNF level was unaltered between aggressive and nonaggressive rats. In the frontal cortex of nonaggressive rats increased pro-BDNF level was found but BDNF protein level was also undetectable.

The results demonstrates that BDNF and pro-BDNF contributes to the genetically defined aggressiveness in rats.

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Poster 38

The effects of TC-2153 on behavior, serotonin system and BDNF in mice with different predisposition to catalepsy.

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Mental disorders are the most disabling medical illnesses. In the Novosibirsk Institute of Organic Chemistry the

psychotropic drug 8-(trifluoromethyl)-1,2,3,4,5-benzopentatiepin-6-amine (TC-2153) with very low acute toxicity was synthesized.

Here we studied the acute effects of TC-2153 (10, 20, 40 mg/kg, per os) in the forced swim (FST), open field (OFT), plus-maze (PMT) tests and catalepsy and the chronic effect (10 mg/kg/day, per os, for 14 days) on behavior and the expression of genes encoding Brain-derived neurotrophic factor (BDNF) and the serotonin system (5-HT1A serotonin receptor (*Htr1a*), monoamine oxidase A (*Maoa*), serotonin transporter (*Slc6a4*) and tryptophan hydroxylase 2 (*Tph2*)) in the brain of mice.

It was shown, that acute and chronic TC-2153 administrations produced anticataleptic effect. We showed that acute TC-2153 produced antidepressant effect in the FST. Comparison of behavioral effects of TC-2153, imipramine and fluoxetine (20 mg/kg, acute) showed, that TC-2153 produced similar antidepressant effect in the FST, without visible negative side effects in the OFT and PMT.

The chronic TC-2153 administration didn't change the gene expression of *Tph2* and *Slc6a4* in midbrain, but decreased *Maoa* and *Htr1a* gene expression in this structure, but not in hippocampus and cortex as well as increased Bdnf gene expression in the hippocampus, but not in midbrain and cortex.

Thus, the serotonin system and BDNF are involved in the mechanism of TC-2153.

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Poster 39

Gene expression diversity in the ventral tegmental area, substantia nigra and subthalamic nucleus

Thomas Viereckel[1], Stefano Pupe[1], Julia Pedersen[1], Nadine Schweizer[1], Casey Smith-Anttila[1], Sylvie Dumas[2], Åsa Mackenzie[1]

With increasing knowledge of the cellular complexity of the midbrain, the need for tools to specifically target subpopulations of cells in restricted areas of the midbrain grows steadily. Current studies usually focus on neurotransmitter-specific transgenic mouse lines to achieve a certain selectivity when investigating the function of midbrain neurons. These, however, are usually spanning the anatomical borders of several different midbrain regions, such as the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). It is therefore almost impossible to selectively target only one of these structures but not the other, using the available neurotransmitter-based transgenic mouse lines. In recent years, several research groups sought to find suitable markers to distinguish VTA and SNc neuronal populations using microarray assays. The bulk of results obtained from these studies, however, stems from adult animals. Since gene expression patterns change throughout development, genes that are expressed solely in one region of the midbrain in the adult might be ubiquitously expressed in young animals.

In this study, we have investigated gene expression differences between the VTA and SNc using microarray analysis of tissue samples collected from these two regions of the midbrain in postnatal day 3 DAT-Cre/tomato mice. We have confirmed the results of the microarray analysis by in situ hybridization assays, both revealing new candidate genes that could serve as basis for highly selective transgenes and confirming the presence of genes discovered in adult tissue based screens in young mice.

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Poster 40

Antisocial behavior and genetic variation in the oxytocin receptor

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Antisocial behavior is a major problem in all societies, and incurs significant public expenditures. The etiology of antisocial behavior is unclear, but it is well-established that genetic variation is a contributing factor. In light of indications that oxytocin may amplify prosocial behavior, dysregulation of oxytocin may consequently play a part in antisocial behavior. The aim of the current study was to investigate whether single nucleotide polymorphisms

(SNPs) in the oxytocin receptor gene (*OXTR*) are associated with antisocial behavior.

A discovery sample was drawn from the Child and Adolescent Twin Study of Sweden (CATSS; n=2372), and the Twin Study of Child and Adolescent Development (TCHAD; n=1232) was used for replication. The participants were assessed for aggressive and non-aggressive antisocial behavior, measured as continuous traits. Eight SNPs in *OXTR* were genotyped. Mixed model statistics were used for all statistical analyses.

In the discovery sample, the rs7632287 AA genotype was strongly associated with higher frequency of overt aggression (directly targeting another individual) in boys (p=6.2^10-7), and this was then replicated in the second sample (p=0.00042). The C allele of rs4564970 was also associated with antisocial behavior in the discovery sample, but we were not able to replicate this in the second sample.

We conclude that the rs7632287 SNP in *OXTR* may influence antisocial behavior in adolescent boys. Further replication of our results, as well as investigations into the underlying mechanisms, could be crucial to understanding how aberrant social behavior arises.

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Poster 41

Socially driven changes in neural and behavioural plasticity in zebrafish

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The ability of an animal to express the appropriate behavioural response depending on social context is a key adaptive ability in group living species. Social plasticity, the capacity of the same individual (same genotype) to generate different behavioural phenotypes can be achieved by different mechanisms of neural plasticity underlying social behaviour. The social decision-making network (SDMN) has been proposed as the core neuronal network that accommodates such behavioural plasticity. This network is composed by two interconnected neural circuits, the social behaviour network and the mesolimbic reward system, that are reciprocally connected. According to this hypothesis, the expression of social behaviour is best represented by the overall activation pattern of the network, rather than by the activity of any of its single individual nodes. In the current work we tested experimentally the SDMN network hypothesis using zebrafish as a model organism. For this purpose, a behavioural paradigm under which male zebrafish consistently express fighting behaviour was used to investigate the effects of different social contexts - winning the interaction, losing the interaction, or fighting an unsolved interaction (mirror image) to unravel the role of perception of fight outcome – on the activation pattern of the SDMN. A subset of nuclei of the SDMN was microdissected and mRNA levels of the immediate early genes (IEG) *cfos* and *egr1* were measured as proxies of neuronal activity. Candidate genes associated with different mechanisms of neural plasticity were also quantified (synaptic plasticity: *bdnf* and *npas4*; neurogenesis: *wnt3* and *neurod*; synaptic maturation: *ngln1*, *ngln2*) to unravel the machinery underlying social plasticity. Our results support the SDMN hypothesis, and indicate that rapid changes in the SDMN occur in response to acute social interactions and different social experiences promote distinct neurogenomic states.

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Poster 42

Laboratory mouse lines derived from outdoor natural selection tested in IntelliCages: reduced initial novel object exploration and prolonged place avoidance

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A natural selection experiment in Russian outdoor pens resulted in mouse lines (MF1 and MF2) differing significantly from randomly mated control mice in the laboratory (MFC), in showing reduced intra/infrapyramidal mossy fiber projections in the hippocampus (IIP-MF). The lines were further bred in Moscow and, after embryo transfer, in Zurich. Standard tests conducted in Moscow with mice from the 15th generation revealed reduced activity of the MF1 and MF2 versus MFC mice in a small openfield, and reduced approaching to a novel object in a small open field in Zurich (18th) generation. MF1, MF2 and MFC mice from the 26th generation were tested in IntelliCage to verify persistence of reduced curiosity and temporal changes in behavior after exposure (i) to a novel object in a corner of IntelliCage, and (ii) for place avoidance after delivering air puffs in corners specific for subgroups of mice. MFC mice spent significantly more time in a corner with a novel object during 7 min than both MF1 and MF2 mice. However, after 24 h both MF1 and MF2 mice had spent significantly more time in that corner. Conversely, visits in a corner delivering air puffs showed a strong and persistent decline in the MF1 and MF2 versus the MFC mice. These data indicate that natural selection altered, together with the IIP-MF distribution, the behavioral phenotype already after the sixth outdoor generation, resulting in persistent behavioral changes reflecting the environmental pressure of a habitat favoring a fearful phenotype associated with retarded novel object exploration.

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Poster 43

Defining global histone 3 lysine 4 trimethylation changes in human alcoholism using ChIP-Seq

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Chronic alcohol abuse is associated with epigenetic changes including DNA methylation and histone modifications that may control long-term changes in gene expression. Histone 3 lysine 4 trimethylation (H3K4me3), a promoter-enriched chromatin (epigenetic) mark of actively transcribed genes, is implicated in psychiatric disorders including drug addiction. Alcohol abuse results in a general increase in H3K4me3 levels in brains of alcoholics compared to control cases, which is associated with up-regulation of several synaptic genes (Ponomarev et al., J.Neurosci., 2012). Here, we used chromatin immunoprecipitation followed by next generation sequencing (ChIP-Seq) in postmortem human brains of eight alcoholics and eight controls to define specific genes showing differential abundance of the H3K4me3 mark in their promoters. Samples from superior frontal cortex were treated using a modified ChIP protocol and DNA pulled down with an H3K4me3 antibody was isolated and sequenced using the Illumina HiSeq 2500 Sequencer (2 x 100 bp; 20-30 million reads per sample). Non-immunoprecipitated DNA was used as input control. We identified a total of 2260 H3K4me3 peaks (in 1183 known genes) differentially regulated between the groups (n=874 down-regulated, n=1386 up-regulated in alcoholics vs. controls, $p< 0.05$). Functional enrichment analysis of peak-associated genes identified several functional groups including synapse organization and synapse assembly, with the majority of genes in these groups showing higher abundance of the H3K4me3 in alcoholics. Taking together, these data provide support for the hypothesis that chronic alcohol abuse results in up-regulation of synaptic genes in superior frontal cortex via an epigenetic increase of H3K4me3 in their promoters. We also hypothesize that this increase in synaptic functions is compensatory to the loss of neurons in alcoholic brain. Future studies will focus on the functional role of alcohol-induced epigenetic changes in neuroadaptation and neuropathology.

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Poster 44

Behavioral and epigenetic characterization of alcohol and energy drink interactions

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Since first commercialized in Europe in 1987, energy drinks (EDs) are highly consumed, mainly by young people beginning in the adolescence, and an increasing popular trend is to mix EDs with alcohol. Energy drinks are generally non-alcoholic beverages with a high content in legal stimulant compounds, mainly caffeine and taurine (sometimes with guarana), along with sugar, vitamins and minerals. Here, we aimed to characterize the intake of ED and mixing alcohol/ED (Red Bull®) using operant self-administration procedures and to explore the gene expression profile of histone deacetylases (*Hdac1-11*) in Wistar rats. First, we introduced progressively the ED (20, 40, 60, 80, and 100% v/v), then we conducted a dose response curve for alcohol with ED (3, 6, 9, 15 and 20% v/v), and after that, we investigated the "alcohol deprivation effect" (an experimental model of alcohol relapse) in combination with ED and an extinction/reinstatement procedure (an experimental model of cue-induced craving). Throughout the experiments we used a control group drinking sucrose (11% w/v, the amount of sugar found in ED). In addition we examined alcohol, caffeine, taurine, insulin, glucose levels in peripheral blood in vivo. Finally, the animals were sacrificed for the analysis of histone deacetylases gene expression in the brain (prefrontal cortex and amygdala), heart and liver, among other tissues. One of the main findings was that the combination of alcohol and ED lead to a significant increase of alcohol consumption. All the results will be presented and fully described in the 2015 IBANGS meeting.

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Poster 45

A translational study of alcohol binge in rats and humans: gene expression profiling of histone deacetylases in blood

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This study aimed to characterize *Hdac1-11* gene expression in the rat peripheral blood, liver, heart, prefrontal cortex and amygdala after repeated alcohol binges, and to determine the parallelism of *Hdac* gene expression between rats and humans in peripheral blood. For this purpose, we examined *Hdac* gene expression following 1-, 4- or 8-alcohol binges (3g/kg) in the rat, in patients who were admitted in the hospital emergency department for acute alcohol intoxication, and in a rat model of daily operant alcohol self-administration. We found that: (a) acute alcohol binge reduced gene expression in the rat peripheral blood (*Hdac1-10*), being attenuated this effect after repeated alcohol binges. In liver, there was also a reduction (*Hdac2,3,4*) but an increase in heart (*Hdac1,7,8*) and amygdala (*Hdac1,2,5*); (b) there were some correlations in gene expression among tissues; (c) an increase of blood alcohol concentrations 1-4 hours after repeated alcohol binges, (d) only the 8-alcohol-binges group developed hepatic steatosis (fatty liver); (e) in humans, alcohol binge increased *HDAC* gene expression in peripheral blood (except for *HDAC9, 10*); and (f) daily operant alcohol self-administration in rats increased *Hdac* gene expression in blood similarly to that observed in human. Our results suggest that an increase in *HDAC* gene expression in peripheral blood is associated to an experienced drinker whereas a reduction would be linked to the first exposures to alcohol.

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Poster 46

Embryo-larval stress exposure modifies behaviour ontogeny and genes expression in zebrafish.

Sandie Millot[1], Lucette Joassard[1], Marie-Laure Bégout[1], Xavier Cousin[2]

Perinatal stress has been reported to affect numerous functions, including behaviour, in later stages. The main purpose of this study was to identify how embryo-larval stress modifies behaviour ontogeny. To this aim, early stress effects have been analysed by combining complementary approaches on zebrafish. Embryo were exposed just after fertilisation and until 4 days post fertilisation (dpf), to a natural stress molecule (alarm cue, AC), to an artificial aversive molecule (cysteine), or nothing (control). At 6 dpf, 1 and 2 months individuals were tested for exploration capacities in a new environment, environmental choice (dark *vs* bright), photomotor responses (PMR) and neophobia (novel object). At each life stage, individuals were sampled for measuring whole body cortisol concentration, monoamines quantification and genes expression (*c-fos, egr1, acth* and *crf*). Early exposure to AC induced an increased anxiety in 6 dpf larvae, 1 and 2 months old juveniles characterised by strong thigmotaxic and scotophobic behaviours and high swimming activity changes during tests. Cysteine induced a weaker increase which was only observed in 6 dpf and 1 month old individuals suggesting a gradation of response or the activation of different pathways. The latter hypothesis is supported by molecular analysis which showed a significantly higher activation of *c-fos* and *egr1* expression in 6 dpf AC larvae compared to cystein and control. In conclusion, these results revealed zebrafish as a good model to analyse late consequences of perinatal stress and to characterise underlying molecular mechanisms.

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Poster 47

Brain weight and behavioral differences in mouse strains selected for different brain weigh after the selection stopped

OV Perepelkina, AYu Tarasova, VA Golibrodo, IG Lilp, Il Poletaeva

The selection of laboratory mice for large and small relative brain weight was performed several times by different investigators. Such selection usually resulted in the appearance of reliable brain weight differences after a few selection generations. Differences in behavior emerged as well. The brain weight differences Large vs Small Brain (LB and SB) lines was about 16-18% of the mean value. In current experiment starting from F22 the selection was discontinued and both lines were bred randomly. The highly significant relative brain weight differences persisted in these generations. Behavioral differences between these strains were also found. In F28 the reaction to 12% i.p. ethanol injections (2.4 mg/kg) was analyzed. Control LB's explored new box more actively and were less affected by stressful environment than SBs. SB ethanol mice were less anxious in EPM than controls, they started exploration of closed +-maze earlier, moved more actively than saline injected mice. Behavioural changes after ethanol were not so clear in LB mice, although their locomotion level increased. In F32 the effects of i.p. injections of methylglyoxal (MG) were tested and differences between groups were also found. In summ the MG injections in SB mice induced the paradoxical changes which could be described as anxiogenic effects, while practically no changes were noted in LB mice after MG treatment.

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Poster 48

Zebrafish quaking genes are associated with nervous system development

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The Quaking protein (QKI) is an RNA-binding protein involved in post-transcriptional mRNA processing. It has been found to be both essential for embryonic development in mice and has been associated with several human neurological disorders. As a knockout of *Qk* is embryonic lethal in mice, we investigated the use of zebrafish to help delineate the function of QKI in early development. We have examined the spatiotemporal profiles of the three *qki* genes (*qkia*, *qkib*, and *qki2*) and applied both morpholinos and CRISPR/Cas9 with a variety of transgenic zebrafish, allowing specific cell populations to be studied *in vivo*. Evolutionary analyses have also helped resolve the appearance of three qki genes in the zebrafish, in contrast to the single human QKI gene.

We have found distinct spatiotemporal expression profiles for each gene. Both *qkib* and *qki2* show unique, yet partially overlapping expression within the central and peripheral nervous system, largely confined to areas of proliferative activity, and distinct from neuronal cells. Alongside the evolutionary analysis, this suggests that a subfunctionalisation of the three genes has emerged. Morpholino knockdown suggests that both *qkib* and *qki2* play a critical role in the proper development of the peripheral nervous system, while qkib is required for cerebellum formation.

Overall, we suggest that the zebrafish is a suitable model system in which to study the qki genes throughout development, and find discrete spatiotemporal expression, yet a consistently crucial role in nervous system formation.

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Poster 49

An InSciEd Out Intervention in Adolescent Mental Health

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Mental health and addiction are ranked fifth for 2010 global disease burden and first for disability impact. The burden of mental illness is particularly high in adolescents due to early onset and low efficacy of existent interventions. This project harnesses the translational spectrum of mental health and addiction research from bench to community to develop methods for improving adolescent mental health outcomes. Our approach considers refinement of conceptual boundaries between mental health and addiction with those of barriers to mental health help-seeking for interventions in adolescents. We hypothesize that fuller integration of basic, translational, and clinical sciences will bring about positive adolescent mental health outcomes. We are probing the crossover between mental health and addiction via a high-throughput drug-repurposing screen in zebrafish for application of existing mental health pharmaceuticals in nicotine cessation. The premise of this bench science is concurrently queried in human communities via a global survey for demographic correlates of adolescent mental health and addiction. To date, ~1,575 students have been sampled in three demographically diverse Indian schools. The intervention component of this work begins in educational "basic science" through assessment of a novel science and education partnership program on health literacy. A case study school provides longitudinal analysis of statistically significant science knowledge gains in students from grades 5 to 8. Application of this program in a framework called Prescription Education has generated mental health curriculum for an intervention bridging knowledge-understanding-attitudes-intents-behavioral change.

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Poster 50

Effects of Nalmefene on alcohol and co-administration of cocaine

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Nalmefene is a mu- and delta-opioid receptor antagonist and a kappa-opioid receptor partial agonist. Recent studies in humans and animal models are indicating that nalmefene would be a promising treatment for alcohol abuse. In fact, nalmefene was approved for the reduction of the alcohol consumption in alcohol-dependent adults in Europe in 2013. However, the effects of nalmefene on the co-administration of alcohol and cocaine remain largely unknown. Here, we tested first different concentrations of nalmefene administered subcutaneously (s.c., 0.01, 0.05 and 0.1 mg/Kg) and orally (p.o., 10, 20 and 40 mg/Kg) in Wistar rats undergoing operant alcohol self-administration. Then we studied the effects of nalmefene in co-administration with cocaine at a dose of 20 mg/kg i.p., which we have demonstrated that increases significantly alcohol consumption. The psychomotor effects of nalmefene before alcohol self-administration and cocaine exposure were examined. Blood samples were collected to analyse alcohol and cocaine metabolism (blood alcohol levels and benzoylecgonine). Quantitative real-time PCR was used to characterize the gene expression of histone deacetylases (*Hdac1-11*) and other genes implicated in the metabolism of alcohol and nalmefene. The tissues examined included brain, heart, liver and kindney. As far as this is an ongoing experiment the final results will be shown for the first time in the 2015 IBANGS meeting.

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Poster 51

Epigenetic modulation of long-term neuroadaptation to alcohol by the histone acetyl-transferase CBP

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Alcohol exposure triggers adaptations in the brain that lead to the development of tolerance and dependence. These adaptations are believed to be of central importance in producing the addictive state and have been shown to persist for relatively long periods of time. In Drosophila, a single exposure to alcohol results in a prolonged increase in alcohol resistance and withdrawal symptoms that extends over several days. The persistent nature of these adaptations suggests that the mechanisms behind them involve long-lasting changes in gene expression and may include the epigenetic restructuring of chromosomal regions that perpetuate them. Epigenetic histone modifications have recently emerged as important modulators of gene expression and are thought to orchestrate and maintain the expression of multi-gene networks. In Drosophila, tolerance to alcohol is mediated in part through the activity of a cohort of interconnected pre-synaptic genes that display a dynamic increase in histone H4 acetylation across their transcriptional control region. However, the molecular mediator of the acetylation process remains unknown. Here we show that the Drosophila histone-acetyl transferase CBP, which is encoded by the gene nejire, mediates the histone H4 acetylation required for gene regulation during the development of drug tolerance. We find, that nejire is both necessary and sufficient for the development of tolerance to alcohol, as a mutation that reduces nejire expression also reduces tolerance, whereas expression from an inducible nejire transgene mimics tolerance in naive animals. We propose that CBP regulates gene expression by the targeted acetylation of specific gene promoters.

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Poster 52

The Influence of ADOLESCENT Nicotine exposure on Alcohol Consumption and gene expression

Helen M. Kamens

Adolescence is a crucial time for brain maturation that coincides with the initiation of alcohol and cigarette use. Research indicates that smokers are more likely to consume heavy quantities of alcohol. The aim of this study was to examine how adolescent nicotine exposure influences alcohol consumption in female C57BL/6J

mice and to examine gene expression differences that may drive this effect. Briefly, during a nicotine-treatment phase, adolescent mice (PND 34 +/- 3 days) were individually housed and given access to either nicotine (200 micrograms/mL) or water for 22 hours a day. Water was available to all animals for the remaining 2 hours (starting 3 hours after lights off). After 6 days of nicotine exposure, the 4-day ethanol drinking-in-the-dark (DID) protocol begun. Briefly, during the 2 hours when nicotine was not available, a single bottle of 20% ethanol was presented. After 2 hours of ethanol exposure, mice were returned to their previous regimen of water or nicotine. On the final day mice had access to ethanol for 4 hours before tail blood was collected to assay blood ethanol concentration (BEC) and whole brains were dissected to isolate RNA for whole transcriptome analysis. C57BL/6J mice given access to nicotine during adolescence had significantly greater ethanol consumption as evidenced by increased BECs compared to subjects who had water. Analysis of whole brain gene expression indicated that this behavioral change was accompanied by a reduction of differentially expressed genes. These data indicate that adolescent nicotine exposure increases alcohol consumption and that alterations in gene expression may mediate this effect.

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Poster 53

Essential roles for the splicing regulator nSR100/SRRM4 during nervous system development

Mathieu Quesnel-Vallières[1,2,3], Manuel Irimia[2,4], Sabine P. Cordes[1,3,5], and Benjamin J. Blencowe[1,2,5]

Alternative splicing (AS) generates vast transcriptomic complexity in the vertebrate nervous system. However, the extent to which trans-acting splicing regulators and their target AS regulatory networks contribute to nervous system development is not well understood. To address these questions, we have generated mice lacking the vertebrate- and neural-specific Ser/Arg-repeat related protein of 100 kDa (nSR100/SRRM4). Loss of nSR100 impairs development of the central and peripheral nervous systems, in part by disrupting neurite outgrowth, cortical layering in the forebrain, and axon guidance in the corpus callosum. Accompanying these developmental defects are widespread changes in AS that primarily result in shifts to non-neural patterns for different classes of splicing events. The main component of the altered AS program comprises 3-27 nucleotide neural microexons, an emerging class of highly conserved alternative splicing events associated with the regulation of protein interaction networks in developing neurons and neurological disorders. Remarkably, inclusion of a six-nucleotide nSR100-activated microexon in Unc13b transcripts is sufficient to rescue a neuritogenesis defect in nSR100 mutant primary neurons. These results thus reveal critical in vivo neurodevelopmental functions of nSR100, and they further link these functions to a conserved program of neuronal microexon splicing.

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Poster 54

The neurobiological basis of antisocial behavior: Insights from a molecular genetic family based association study

AD Lordos[1], GP Zacharaki[1], KA Fanti[1]

While psychophysiological and neuroimaging studies suggest a significant biological contribution to antisocial behavior (AB), the underlying neural mechanisms remain to be elucidated. Molecular genetic studies may shed light on the issue, by identifying genotypic variants which are associated with the AB phenotype and then tracing the likely downstream neurobiological impact of such variants. In practice, however, few candidate gene association studies related to AB that focus on whole neurobiological systems have yet been conducted. In the current study, a sample of 200 adolescent-mother-father trios in the community were measured on levels of AB as well as relevant endophenotypes of AB, specifically Executive Dysfunction (EDF) and Callous Unemotional Traits (CU). Furthermore, saliva samples were taken from each participant, for extraction of genomic DNA. Currently, DNA is being isolated from the saliva samples for later genotyping to screen for polymorphisms across multiple candidate genes which impact distinct neurobiological systems. This includes catecholamine

genes, serotonergic genes, cholinergic genes, glutaminergic genes, GABA genes, oxytonergic genes, neurodevelopmental genes, and genes that affect functional neuronal connectivity. Results will be analyzed using the Family Based Association Testing (FBAT) technique. Structural Equation Modeling will be used to test direct and mediated relationships between cumulative genetic risk for each neurobiological system, the relevant endophenotypes, and finally AB. It is expected that the results will reveal distinct associations between specific neurobiological systems' impairment and AB, mediated either by EDF or by CU – thus shedding light on the underlying neurobiology of AB and its heterogeneous variants.

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Poster 55

Do Autism and Callous Unemotional Traits (CU Traits) possess a shared molecular genetic background?

GP Zacharaki[1], VM Theocharous[1], AD Lordos[1], KA Fanti[1]

It is well known that one of the functional difficulties of people with autism and people with CU traits (an aspect of psychopathy) is the quality of their social interactions and more generally their social adjustment. Furthermore, both autism and CU Traits tend to be present from early childhood, both involve empathy deficits, and both are often comorbid with aggression. More recently, associations between both conditions and oxytocin receptor gene polymorphisms have been reported in the literature. Despite these similarities, few studies have considered the possibility that autism and CU Traits may possess a shared genetic and neurobiological background. A more specific and intriguing hypothesis might be that well-characterized autism genes can also inform explanatory models for CU Traits – a field where the molecular genetic literature is still at a nascent stage. To investigate this possibility, data was collected from a sample of 200 community adolescents and their parents. CU Traits were measured through the self-reported Youth Psychopathic Traits Inventory, as well as through clinical interview with parents, while saliva samples were collected from all participants. Extracted DNA is currently being genotyped to test for common polymorphisms across multiple genes that have been reported in the literature to be associated with autism – including genes involved in the regulation of oxytocin, the neurexins/neuroligins, the estrogen receptors, integrin genes, the reelin gene, and genes that code for calcium channels. Association between these genes and CU Traits will be investigated using FBAT, while findings and implications will be presented at the conference.

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Poster 56

Elucidating Cannabinoid Biology in Zebrafish

Krug, R.G., II, Petersen, M.O., Clark, K.J.

Although the number of annual cannabis users exceeds 100,000,000 globally and an estimated 9% of these individuals will suffer from dependency, a dearth of knowledge exists about the potential consequences on public health. However, the psychoactive constituents of cannabis are known to signal through the endocannabinoid (eCB) system, and to disrupt features of vertebrate physiology and behavior. While studies have revealed that the eCB anandamide (AEA) regulates stress response system (SRS) activity, little is known about the pathological consequences of disrupted AEA signaling. Our central hypothesis is that disruptions in the AEA signaling system have pathological consequences on vertebrate behavior and physiology, including dysregulation of the SRS. Herein, we use a preclinical zebrafish model to clarify the ramifications of disturbances in the AEA signaling system. Using qRT-PCR and *in situ* hybridization we show that the genes encoding enzymes that synthesize (*abhd4, gde1, napepld*), enzymes that degrade (*faah, faah2a, faah2b*), and receptors that bind (*cnr1, cnr2, gpr55-like*) AEA are expressed throughout development. We show that disruptions of this system via exogenous cannabinoid administration results in altered behavior and physiology, including increased secretion of glucocorticoids in our stress response reporter line. We are developing a zebrafish AEA signaling mutant library using transcription activator-like effector nucleases (TALENs). Currently, we are identifying our first mutant lines and will share the preliminary results of behavioral assays using our first mutants. Collectively, these results establish zebrafish as a viable model for studying AEA signaling, and lay a foundation for informing a better understanding of the toxicological and therapeutic potential of the eCB system.

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Poster 57

QTL mapping of binge eating to the Cyfip2 locus in C57BL/6 substrains: Implications for hyperphagia in Prader-Willi Syndrome

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Eating disorders are heritable and lethal and exhibit a lifetime prevalence of 1 to 3%; however, the genetic factors have not been identified. Mammalian model organisms offer a powerful approach to studying the genetic and biological basis of heritable behavioral symptoms such as binge eating that define the disorders. We developed a model of binge eating and conditioned reward using a conditioned place preference (CPP) procedure whereby outbred CFW mice exhibited a nine-fold escalation in palatable food (PF) and PF-CPP. The progressive escalation in food consumption coincided with an escalating, nearly perfect correlation with PF-CPP, thus assigning increasing motivational value behind each binge episode. We identified robust C57BL/6 substrain differences in binge eating and conditioned food reward whereby the C57BL/6NJ (NJ) inbred strain, but not the C57BL/6J (J) strain, showed a robust escalation in PF consumption, PF-CPP and conditioned locomotor activity. QTL mapping of binge eating in J x NJ-F2 mice revealed a major QTL on chromosome 11 (LOD = 5) that maps precisely to the *Cyfip2* locus on chromosome 11 – a gene previously identified from this cross that influences psychostimulant behaviors (Kumar et al., 2013). RNA-seq analysis of the striatum is underway to aid in identifying the neurobiological mechanisms that bridge genetic variation with behavior. Interestingly, the closely related homolog of *Cyfip2* (a.k.a. cytoplasmic FMR1-interacting protein 2) - *CYFIP1* - resides within the proximal end of the Prader-Willi Syndrome locus (15q11-q13), providing a clear and testable hypothesis that *CYFIP1* deletion mediates extreme hyperphagia in this syndrome.

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Poster 58

Early environmental enrichment generates stress resilience and more optimistic chicks.

J Zidar[1] and H Løvlie[1]

Affective states (i.e. emotions) of animals are important indicators of animal welfare. Positive emotions, such as satisfaction and security can therefore be used as indicators of positive welfare. Even though effective states are not easily measured, a test scoring 'cognitive judgment biases' has been successfully used to score variation in optimism. By associating one cue with a positive experience (receiving a reward), while another cue is associated with absence of reward, we obtain information about affective states by subsequently observing individuals' response to intermediate, ambiguous cues. Animals in positive emotional states respond to the ambiguous cues as if they predicted a positive experience (i.e. optimistically).

Here we scored the emotional states of domestic fowl (*Gallus gallus domesticus*), raised under enriched or impoverished conditions. Cognitive judgment bias tests were performed before and after exposing chicks to a battery of stressors. Prior to being stressed, the emotional states did not differ between individuals from the two groups. However, chicks in enriched conditions showed better resilience to stress by being more optimistic in the subsequent cognitive judgment bias test, compared to chicks in impoverished conditions. This suggests that environmental complexity early in life can buffer against responses to future stress and that environmental conditions can influence the emotional state of birds. Our results demonstrate that environmental factors can be used to stimulate positive welfare in animals. The underlying variation in the monoaminergic systems (serotonin and dopamine) will be explored to further our understanding of what generate positive and negative affective states.

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Poster 59

Measuring conditioned fear in Diversity Outbred mice

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The success of genome-wide association studies (GWAS) in humans has stimulated interest in utilizing genetically diverse, highly recombinant mouse populations. These characteristics allow for the opportunity to observe a wider range of phenotypic variation, offer greater mapping precision, and thus increase the potential for efficient gene identification. We used JAX Diversity Outbred mice (DO) to fine-map quantitative trait loci (QTLs) associated with conditioned fear (CF). 398 DO mice were tested for acquisition, extinction, and renewal of CF using a three-day protocol. A one-way repeated measures ANOVA demonstrated that freezing was negligible at baseline and significantly increased across conditioning trials, ($F_{3, 315}$ = 241.4, $p < 0.0001$). During extinction training, freezing significantly decreased across trial-blocks ($F_{9, 389}$ = 43.52, $p < 0.0001$), suggesting that DO mice were able to extinguish the fearful association over time. On the renewal test, mice displayed less freezing relative to the first trial-block of extinction training ($t(397) = 8.65$, $p < 0.0001$). Importantly, we observed a range of values for these traits. This sort of variability in the population is of the utmost importance, because a successful genetic mapping study requires naturally occurring trait variation in order to search for naturally occurring genetic variation that is associated with it. We obtained genotypes from a subset of these mice at ~78k markers across the genome and performed GWAS. We identified 7 suggestive QTLs associated with CF on chromosomes 4, 5, 10, 11, & 13 (LODs > 5; $p < 0.05$). We continue to increase our sample size to improve mapping power and resolution, and are collecting brain regions for future RNA-Seq experiments that will explore the network of correlations that exist between DNA sequence, gene expression values and CF.

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Poster 60

Associations between genetic variations in *IL1B* and brain region volumes in bipolar patients and controls

Nina Strenn, Erik Pålsson, Mikael Landén, Agneta Ekman

Background: Expression of immune-related genes has been shown to be significantly correlated with grey matter volume in the hippocampus and the caudate1, and differences in grey matter volume in the hippocampus have been associated with variations in interleukin 6 2 and the tumor necrosis factor3. The pro-inflammatory cytokine interleukin 1 beta (IL1B) has been shown to be of relevance for brain function, e.g. in axonal plasticity after spinal cord injury4 as well as hippocampal synaptic plasticity in animal studies5.

Aim: The aim of this study was to investigate associations between genetic variations in *IL1B* and brain region volumes in bipolar patients and controls.

Methods: Genotyping of single nucleotide polymorphisms (SNPs) was conducted using the Kompetitive Allele Specific (KASPar®) PCR SNP genotyping system (Kbiosciences, Herts, UK) in DNA extracted from blood samples from controls and patients. Magnetic resonance imaging scans were acquired at the MR Research Centre, Karolinska University Hospital, Stockholm. The study was approved by the Ethics committee, Stockholm, Sweden.

Results: We found significant associations between SNPs in *IL1B* (rs16944, rs1143623, rs1143634 and rs1143627) and grey matter volume in several of the investigated brain areas, such as putamen. No significant differences were seen in the distribution of the genotypes when comparing patients with controls.

Conclusion: Our findings that variations in *IL1B* are associated with changes in grey matter volume of several brain regions are in line with studies showing associations between variations in *IL1B* and changes in grey matter volume in patients with bipolar disorder6 as well as in schizophrenic patients7.

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Poster 61

Effects of maternal diet during the perinatal period on gene expression and behavior in mice

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Nutritional deficiencies during the perinatal period have been linked to increased risk for development of psychiatric disorders in the human population and have been modeled in rodents and result in behavioral changes. The mechanism in both humans and animal models is believed to be epigenetic changes that alter gene expression.

We designed an experiment to examine the effects of maternal dietary modifications on various genetic backgrounds to study alterations in behavior and gene expression in mice. We utilized a disjoint reciprocal diallel with 16 Collaborative Cross (CC) mouse lines crossed to produce recombinant inbred intercross (RIX) mice. Females from each line are exposed to one of four diets (vitamin D and protein deficient, methyl enriched and standard) prior to mating and throughout gestation and weaning. Adult female offspring are either tested in behavioral assays to measure stress response, anxiety- and depressive-like behaviors or whole brain gene expression analysis using RNA-Seq. Comparison within reciprocals and across CC-RIX lines will reveal genetic, diet, parent-of-origin and diet-specific parent-of-origin effects.

We have nearly completed breeding and phenotyping of all CC-RIX offspring, with over 600 mice tested for behavior and gene expression assessed in 96 samples. We have identified significant strain, parent-of-origin, and diet effects on behavior and are in the process of analyzing the gene expression data and identifying possible candidate genes that interact with diet during development to change behavior in adult offspring for validation and further testing.

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Poster 62

Developing zebrafish methodology to model genetic and environmental modifiers of the vertebrate stress response system (SRS).

Tanya L. Poshusta, Han B. Lee, Randall G. Krug II, Karl J. Clark

Stress-induced changes in brain function and physiology contribute to many complex disorders, including neuropsychiatric disorders—a major cause of disability in the world. Both genetic heritability and environmental factors contribute to the progression of neuropsychiatric disorders, such as major depressive, generalized anxiety, and substance use disorder. These complex multisystem disorders require whole animal models for effective study. The zebrafish (*Danio rerio*) is an ideal animal model for discovery of genetic modifiers of the vertebrate-conserved SRS. We observed that larval zebrafish temporarily increase locomotion release following exposure to an acute, mild hyperosmotic stressor. This behavior correlates with acute changes in cortisol production.

Importantly, mutation of core stress response receptors, including the ACTH receptor (*mc2r*) dramatically alter locomotor stimulation. In addition to the behavioral locomotor assay that measures rapid, "non-genomic" effects of cortisol signaling, we have developed a transgenic reporter that produces a short half-life green fluorescent protein in response to "genomic" activity of the glucocorticoid receptor. We are using a combination of our newly developed assays, fish lines, and genome engineering technology to develop a platform to investigate the vertebrate SRS. Currently, we are using a series of targeted mutations (e.g. *crhr1, crhr2, mc2r, nr3c1*, and *nr3c2*) and pharmacological agents (e.g. CRH, ACTH, and cortisol) in an effort to define how particular mutants or ligands contribute to our behavioral and transcriptional assays to help us place new genetic modifiers within the vertebrate stress response signaling cascade.

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Poster 63

Individualizing the Treatment of Tobacco Dependence by Assessing Behavioral Endophenotypes and Molecular Adaptations in Zebrafish

Margot A. Cousin, Jon O. Ebbert, Jarryd M. Campbell, Karl J. Clark, Stephen C. Ekker, Eric W. Klee.

Cigarette smoking is the leading preventable cause of death worldwide with no successful treatment options for the majority of individuals wishing to quit. A significant proportion of smokers are also heavy drinkers, and the leading cause of death of alcoholics is tobacco-related disease. To improve treatment efficacy and individualize treatment strategies to quit smoking and/or drinking, the etiology of this coincident behavior must be more clearly understood, and the genetic correlates of nicotine/ethanol dependence and treatment response identified.

We use zebrafish to model endophenotypes of nicotine and ethanol addiction, and have developed assays measuring responses associated with acute nicotine and ethanol, varenicline-induced attenuation of the nicotine response, nicotine and ethanol interaction with co-administration and/or pretreatment exposures, and the effect of nicotine/ethanol exposure on nAChR upregulation in adult fish. We've previously identified novel candidate pharmacotherapeutics for tobacco and alcohol dependence, identified genetic loci using forward genetics, and described nicotine and ethanol interaction effect. Here, we describe loss of the alpha4 nicotinic receptor potentiates nicotine-induced locomotion and a stronger varenicline treatment effect, consistent with human pharmacogenetic associations. We also demonstrate chronic nicotine induces upregulation of the nicotinic receptors, consistent with humans and mammalian models. Together these assays provide a multifaceted view of these addictive drugs, and the integration of this data enables us to interrogate the molecular and genetic contributors to the actions of nicotine and ethanol. In doing so, we will be able to identify novel genes implicated in these responses to individualize the treatment of tobacco dependence.

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Poster 64

Alcoholism - Identification of molecular targets by analysis of transcript levels of NA alcohol addiction model

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Alcoholism is a complex disorder influenced by numerous factors like genetic, personality traits, other psychiatric disorders and environment. Although genetic susceptibility to alcoholism is known to be an important factor, the molecular mechanisms remain to be elucidated. Thus, we propose the study of the transcriptome of a mouse model exposed to a free choice treatment.

In this study heterogeneous Swiss mice were housed individually and exposed to a three-bottle free-choice self-administration treatment, consisting of four phases: 1. Acquisition/free choice (10 weeks) of water, ethanol 5% or 10% v/v; 2. Withdrawal of ethanol solutions (2 weeks); 3. Re-exposure (2 weeks); 4. Quinine adulteration of ethanol solutions (2 weeks). A control group had access just to water for the duration of the experiment. Later, mice were classified in three distinct groups according to their drinking behavior: "Addict" (preference for ethanol and high levels of drinking in all phases); "heavy drinker" (preference for ethanol and high levels of drinking in Acquisition phase and a significant reduction in Adulteration phase); "Light drinker" (preference for

water in all phases). Through the microarray technique, we compared the transcriptome of these groups in three distinct brain areas: hippocampus, striatum and prefrontal cortex. The large gene list found was refined through *in silico* enrichment analysis and validated later by qPCR. This approach revealed new candidate pathways potentially involved with the mechanism behind addictive behavior.

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Poster 65

Cellular sexual dimorphism of X and Y homologous gene expression in human central nervous system during early male development

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Renewed attention has been directed to the functions of the Y chromosome in the central nervous system during early human male development, due to the recent proposed involvement in neurodevelopmental diseases and cortical ontogeny. *PCDH11Y* and *NLGN4Y* are of special interest, because they belong to gene families involved in cell fate determination and formation of dendrites and axons. Conventional in-situ detection of these genes is not possible; due to the high sequence identity to the X encoded homologs. We used RNA sequencing, immunocytochemistry and a padlock probing and rolling circle amplification strategy, to distinguish for the first time the in-situ expression of X and Y homologs in human embryos, 8-11 weeks. The most striking result; was that the Y encoded genes are expressed in specific and heterogeneous cellular neural subpopulations that rarely express the X homologs. Our findings suggest that a male-specific cellular network may exist in the embryonic central nervous system.

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Poster 66

SNP array analysis of copy number variants on the human Y chromosome reveals novel and frequent duplications overrepresented in specific haplogroups

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The human Y chromosome is almost always excluded from genome-wide investigations of copy number variants (CNVs) due to its highly repetitive structure. This chromosome should not be forgotten, not only for its well-known relevance in male fertility, but also for its involvement in clinical phenotypes such as cancers, heart failure and sex specific effects on brain and behavior. Affymetrix 6.0 SNP array platform is suitable for identification of gain and loss of Y chromosome sequences. In a set of 1718 males, we found 24 different CNV patterns, many of which are novel. We confirmed some of these variants by PCR or qPCR. The total frequency of individuals with CNVs was 13.9%, including 9.3% with duplications, 4.5% with deletions and 0.1% exhibiting both. Hence, a novel observation is that the frequency of duplications was more than twice the frequency of deletions. Another striking result was that 10 of the 24 detected CNVs were significantly overrepresented in one or more haplogroups, demonstrating the importance to control for haplogroups in genome-wide investigations to avoid stratification. NO-M214(xM175) individuals presented the highest percentage (95%) of CNVs. If they were not counted, 12.3 % of the rest included CNVs, and the difference between duplications (9.4%) and deletions (2.9%) was even larger.

Our results demonstrate that currently available genome-wide SNP platforms can be used to identify duplications and deletions in the human Y chromosome. Future association studies of the full spectrum of Y chromosome variants will demonstrate the potential involvement of gain or loss of Y chromosome sequence in different phenotypes.

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