GBB 2019: GENES, BRAIN AND BEHAVIOR 2019

PROGRAM FOR FRIDAY, MAY 10TH

Days: next day all days

View: session overview talk overview

09:00-16:00 Session 1: Symposium/Workshop

Symposia/Workshop presented by the Simons Initiative for the Developing Brain

17:00-18:00 Session 2: Registration

Registration

17:50-18:00 Session 3: Presidential Welcome

Presidential Welcome

CHAIR: *Catharine Rankin*

18:00-19:00 Session 4: Keynote

Special Lecture

Dr Carmen Sandi

CHAIR: *Wim Crusio*

18:00 *Carmen Sandi*

Mitochondrial function in the nucleus accumbens links anxiety with stress coping behaviors

ABSTRACT. There is important variation in mitochondrial function in the nucleus accumbens that explain anxiety-related differences in social competition. High anxious individuals are highly vulnerable to stress-induced depression. Importantly, high anxious rats display impaired mitochondrial function (respiration, membrane potential, ATP and ROS production) in the nucleus accumbens which is causally implicated in their disadvantage to achieve dominant status. Intra-accumbal infusion of nicotinamide, an amide form of vitamin B3 that boosts mitochondrial function, prevents the development of subordinate status in high anxious rats. Manipulations that modify anxiety levels transiently, such as acute stress or diazepam treatment, modulate social competitiveness and accumbal mitochondrial function. Notably, diazepam treatment when given either systemically or into the ventral tegmental area enhances accumbal mitochondrial respiration

and ATP production along with increasing dominance behaviors. Furthermore, dominant mice show higher levels in accumbal energy-related metabolites than subordinate mice, as well as increased vulnerability to show social avoidance following social defeat. In subordinates, but not dominants, levels of these metabolites increase following chronic social defeat stress. Our findings have implications for the understanding of the mechanisms involved in individual differences in motivated behavior and vulnerability to stress.

Carmen Sandi Brain Mind Institute, Ecole Polytechnique Federal de Lausanne (EPFL), Switzerland

19:00-21:00 Opening Reception

Opening Reception

GBB 2019: GENES, BRAIN AND BEHAVIOR 2019

PROGRAM FOR SATURDAY, MAY 11TH

Days: previous day next day all days

View: session overview talk overview

08:30-09:00 Session 5: Registration

Registration

09:00-11:00 Session 6: Symposium 1

Genetics & neurobiology of disordered eating

CHAIR: *Camron Bryant*

09:00 *Sarah Mak*

Elucidation of Secretin in thirst regulation within subfornical organ neurons in the brain

ABSTRACT. Precise regulation of plasma osmolality is critical in all terrestrial animals to maintain a constant internal environment and prevent continual water loss. Dysregulation of water homeostasis can result in life-threatening disorders including congestive heart failure and cerebral trauma. Secretin (SCT), a classical gastrointestinal hormone, has been newly described as an osmoregulatory neurohormone that modulates hyperosmolality-induced water drinking behaviour and vasopressin (Vp) release in the hypothalamus. Yet, its molecular mechanism and neural circuitry within the osmoregulatory brain centres is still ripe for exploration. When plasma osmolality changes, subfornical organ (SFO) acts as the first station to detect the changes and transduce them into neuronal signals to other brain regions for corresponding responses. Previous data have shown a wide expression of SCT and its receptor (SCTR) in SFO, and dehydration would increase this expression in SFO. Therefore, we hypothesized that SCT may serve as a neurotransmitter in SFO and modulate water drinking behaviour and Vp release. In this study, we established two specific conditional knockout mice models (SCTSFO-/- and SCTRSFO-/-) to elucidate the role of SCT/SCTR in SFO and investigate its downstream pathway regarding dehydration-induced water intake. We found a marked reduction of water intake in both SCTSFO-/- and SCTRSFO-/- mice (72% drop,

p=0.0015; 65% drop, p=0.0387 v.s. sham control) under water-depleted condition. Dehydration-induced cFos expression in SFO was abolished if SCT and SCTR were locally deleted. Thus, current data adds a new piece of information into SCT-mediated osmoregulatory mechanism and may also provide new insights into curing water balance disorders.

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09:20 *Camron Bryant*

Forward genetic and gene validation studies of binge-like eating in mice: Sex-sensitive genetic loci, including male-specific linkage with the Tas2r locus

ABSTRACT. Eating disorders, including binge eating disorder, bulimia nervosa, and anorexia nervosa are highly lethal, heritable disorders with psychiatric and metabolic components. However, the genetic basis of binge eating is completely unknown. Discovery-based genetic and genomic studies in rodents complement human GWAS and can inform genes, networks, and biological pathways underlying maladaptive feeding. We mapped and validated Cyfip2 as a causal genetic factor underlying binge-like eating (BE) in a Reduced Complexity Cross (RCC) and extended these findings to Cyfip1 where we found complex, sex-specific, parent-of-origin selective effects of Cyfip1 haploinsufficiency on BE. In extending our BE model toward additional genetic crosses, we report robust inbred strain differences in BE and conditioned reward between C57BL/6J and DBA/2J strains in our intermittent, limited access, conditioned place preference paradigm. Candidate locus analysis in F2 mice (N=133) identified a male-specific association of the Tas2r locus on chromosome 6 (133 Mb) with escalated BE. Subsequent genome-wide analysis of BE in the same mice with 3K markers confirmed male-specific genome-wide significant linkage on chromosome 6 (LOD=6.0) and resolved the peak location to 53 cM [113 Mb; 48-59 cM). We also identified a sex-averaged QTL on chromosome 5 [peak=28 cM (53 Mb); LOD=5.2; 21-58 cM), and a female-sensitive QTL on chromosome 8 [LOD=4.1; peak=53 cM (109 Mb); 52-59 cM]. The emerging sex-sensitive genetic architecture of BE in mice

has important implications for human GWAS and future therapeutics. Future studies will determine the role of sex hormones and sex chromosomes in the genetic architecture of BE.

Camron D. Bryant1, Richard K. Babbs1, Emily Yao1, Melanie M. Chen1, Julia C. Kelliher1, Julia L. Scotellaro1, Kimberly P. Luttik1, Qiu T. Ruan1,2, Megan K. Mulligan3

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09:45 *Stephanie Dulawa*

Dopamine D2 receptor overexpression in the nucleus accumbens core indirect pathway increases activity-based anorexia selectively in female mice

ABSTRACT. Anorexia nervosa (AN) is an eating disorder observed predominantly in females that is characterized by hypophagia, weight loss, and compulsive exercise. Increased dopamine D2/D3 receptor binding in the anteroventral striatum has been previously reported in AN. Activity-based anorexia (ABA) refers to the hyperactivity and hypophagia exhibited by rodents exposed simultaneously to running wheels and scheduled feeding, and provides a rodent model for maladaptive behaviors in AN. We virally overexpressed D2Rs on indirect striatal pathway neurons of the nucleus accumbens (NAc) core (D2R-OENacInd), which endogenously express D2Rs, and tested mice of both sexes in the open field and ABA paradigms. D2R-OENacInd did not alter baseline bodyweight, but increased locomotor activity in the open field across both sexes. In addition, D2R-OENacInd mice of both sexes consumed more food than controls when food and running wheels were continuously available during the baseline period of the ABA paradigm. Yet paradoxically, when food was available only 7 hours a day during the restriction phase of ABA, female, but not male, D2R-OENacInd mice showed robust reductions in food intake and survival. Female D2R-OENacInd mice also showed reduced bodyweight, increased wheel running activity, and increased food anticipatory activity. The only effect of D2R-OENacInd on male mice during restriction was a

small increase in wheel running, which began late in the restriction period. Our findings indicate that D2R-OENacInd selectively increases ABA behavior in female, but not male, mice. D2R-OENacInd may play a causal role in the maladaptive feeding and exercise behaviors observed in AN patients.

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10:10 *Christina Wierenga*

Taste reward circuitry in women remitted from anorexia nervosa and bulimia nervosa: hunger, satiety, and the motivation to eat

ABSTRACT. Eating disorders are serious and difficult-to-treat psychiatric disorders that may involve altered motivation to eat. Typically, hunger enhances, while satiety decreases, reward sensitivity, yet individuals with anorexia nervosa (AN) restrict eating despite emaciation, and individuals with bulimia nervosa (BN) engage in episodes of binge eating, marked by loss of control and eating despite fullness. In a series of studies, we investigated whether AN and BN are associated with abnormal food reward response when hungry and fed in a neural circuit involved in translating taste signals into motivated behavior. Twenty-six women remitted from AN (RAN; to reduce confounding effects of malnutrition), 26 women remitted from BN (RBN) and 22 control women (CW) were administered water and sucrose during 2 counterbalanced fMRI visits, one after a 16-hr fast and one after a standardized breakfast. As expected, CW were more responsive to taste when hungry versus fed. Group (RAN, CW) x Condition (hungry, fed) interactions in the ventral caudal putamen and insula indicated RAN had a decreased brain response when hungry. In contrast, Group (RBN, CW) x Condition (hungry, fed) interactions in the ventral caudal putamen and amygdala indicated increased CW brain response when hungry, but RBN response did not differ between conditions. RBN also responded more than CW in the amygdala when fed. Failure to integrate taste information with motivational (ventral caudal

putamen [in AN and BN], amygdala [in BN]) and homeostatic (insula [in AN]) drives may promote food avoidance and diminished drive to eat in AN and binge eating in BN.

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10:35 *Christopher Huebel*

Genome-wide association study of anorexia nervosa implicates metabolic and psychiatric origins

ABSTRACT. Anorexia nervosa (AN) is a severe eating disorder characterised by pathological eating behaviour and in certain cases by higher physical activity accompanied by low body fat and fat-free mass. Over the last two decades, family and twin studies have shown that AN has a considerable heritable component with heritability estimates ranging from about 40 to 60%. Genome-wide association studies (GWASs) have yielded eight independent genomic loci associated with AN and its single nucleotide-based heritability has been estimated at 11-17%, indicating a polygenic trait. Analyses partitioning the heritability indicated the involvement of central nervous tissues and cell types in AN. Bivariate linkage disequilibrium score regression (LDSC) can estimate the amount of shared genomics between two traits: Our LDSC analysis showed genomic overlap between AN and psychiatric traits and disorders, such as obsessive-compulsive disorder (OCD), major depressive disorder (MDD), and anxiety, as expected by its clinical comorbidity profile. Surprisingly, AN showed significant negative genetic correlations with anthropometric traits, including body fat percentage and body mass index (BMI), indicating that genomic variants that predispose to lower body mass may also increase liability for AN. Complementing these findings, we also reported genomic overlap between AN and metabolic traits, such as fasting insulin and glucose concentrations as well as high-density lipoprotein concentrations, encouraging a reconceptualization of AN as both

a psychiatric and metabolic disorder. Extending these findings by estimating sex-specific genetic correlations, we were able to demonstrate that body fat percentage in females is more highly correlated with AN than in males, suggesting a set of genomic variants associated with body fat percentage in females also operative in AN that potentially contributes to the extreme sex bias observed in its prevalence.

Christopher Huebel, MD, MSc

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11:00-11:30 Coffee Break

11:30-12:30 Session 7: Outstanding Travel Awardees

Outstanding Travel Awardees

CHAIR: *Mark Rutledge-Gorman*

11:30 *Qiu Ruan*

CLIP-seq analysis of the RNA binding protein hnRNP H in striatum following methamphetamine administration in Hnrnph1+/- mice

ABSTRACT. Hnrnph1 (heterogeneous nuclear ribonucleoprotein H1) is a quantitative trait gene for reduced methamphetamine (MA) behavioral sensitivity. Mice with heterozygous 16-bp deletion in the first coding exon of Hnrnph1 (Hnrph1+/-) showed reduced sensitivity to the stimulant, rewarding, reinforcing effect of MA as well as a decrease in MA-induced dopamine release relative to the wildtype. While accumulating literature indicates a role of Hnrnph1 in neurodevelopment, there is very little known about the mRNA targets of hnRNP H in the brain or the in vivo neurobehavioral function of this RNA binding protein. Given the very modest effects we previously observed on the number of dopaminergic neurons and their forebrain projections, we have since hypothesized that there is an active, drug-induced cell biological mechanism by which Hnrnph1 deletion decreases MA-induced dopamine release and behavior. Therefore, we examined the change in RNA targets of hnRNP H in response to MA. We optimized and performed cross-linking immunoprecipitation coupled with high-throughput sequencing (CLIP-seq) to reveal

hnRNP H-RNA interactions in the striatum (a brain region involved in addiction) of both wildtype and Hnrnph1+/- at baseline and in response to an acute dose of MA (2 mg/kg i.p.). CLIP-seq involves the use of ultraviolet irradiation to generate covalent bond between RNA and proteins that are in close contact. An antibody specific to hnRNP H was used to immunoprecipitate the protein-RNA complex followed by RNA extraction and reverse transcription of the extracted RNA into a cDNA library to be sequenced. This is the first CLIP-seq study to examine drug-induced changes in protein-RNA interactions in a specific, functionally relevant brain region and we expect it will shed light on the molecular mechanisms through which hnRNP H regulates methamphetamine-induced dopamine release and addictive behaviors.

Qiu T. Ruan1,2, Michael A. Rieger3, Jacob A. Beierle1,2, Melanie M. Chen1, Karen Zheng1, Amarpreet Kandola1, W. Evan Johnson4, Joseph D. Dougherty3, and Camron D. Bryant1,2,5

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11:50 *Chi Kin Ip*

Amygdala NPY circuits are critical for the development of accelerated obesity under chronic stress

ABSTRACT. Neuropeptide Y (NPY) exerts powerful feeding related functions in the hypothalamus. However, NPY is also present in extra-hypothalamic nuclei, however their influence on energy homeostasis is unclear. Here we uncover a previously unknown feeding stimulatory pathway that is activated under conditions of stress in combination with calorie dense food with NPY neurons in the central amygdala (CeA) being responsible for an exacerbated response to a combined stress and high fat diet intervention. CeA NPY neuron specific Npy overexpression mimics the obese phenotype seen in a stress/HFD model, which is prevented by the selective ablation of Npy. Using food intake and energy expenditure (EE) as readout we demonstrate that selective activation of CeA NPY neurons results in increased food

intake and a decrease in EE, which requires the presence of NPY. Mechanistically it is the diminished insulin signalling capacity on CeA NPY neurons under stress combined with HFD conditions that leads to the exaggerated development of obesity. Additionally, transcriptome analysis of CeA NPY specific neurons by using translational affinity purification assay (TRAP) with Next-Generation sequencing revealed feeding and stress related markers being dramatically altered during the post-stress period.

Chi Kin Ip1,2, Lei Zhang1,2, Aitak Farzi1,2, Ireni Clarke1, Felicia Reed1, Yan-Chuan Shi1,2, Ronaldo Enriquez 1, Yue Qi1, Chris Dayas3, Bret Graham3, Denovan Begg4, Jens C Brüning5, Diana Hernandez-Sanchez1, Ramon Tasan6, Günther Sperk6 and Herbert Herzog1,2

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12:10 *Emily Petruccelli*

Alcohol causes lasting transcriptomic changes in the Drosophila mushroom body

ABSTRACT. The characterization of dynamic transcriptional responses in specific neurons is key to understanding organismal behavior. RNA sequencing data can help reveal the plasticity and specificity of differentially expressed transcripts and genes. Here, we used Drosophila's genetic accessibility to investigate whether repeated alcohol exposures have long-lasting effects on the active transcriptome of memory-encoding mushroom body neurons, and whether effects change when alcohol is paired with an odor cue. Statistically significant changes were experience-dependent and occurred more at the transcript, and not gene, level. Further gene ontology analysis suggested enrichment for genes known to be alternatively spliced. This suggests that alternative splicing is important for memory encoding and changes after repeated alcohol exposure. The functional implications and specificity of this splicing is currently being

investigated. Ultimately these findings suggest a layer of molecular plasticity through which alcohol could influence memory formation and alcohol-associated behaviors.

1Department of Biological Sciences, Southern Illinois University Edwardsville, PO Box 1651, Edwardsville, IL 62026. 2Washington University in Saint Louis MSTP, Washington University, Box 8226, Saint Louis, MO 63110-1093. 2Department of Neuroscience, Brown University, Box GL-N, Providence, RI 02912.

12:30-13:30 Lunch Break

13:30-15:30 Session 8: Symposium 2

Laterality and cognition

CHAIRS:
Caroline Brennan and *Maria Elena Miletto Petrazzini*

13:30 *Jeremy Niven*

Colony-level lateralisation of forelimb movements in wood ants

ABSTRACT. Lateralised behaviour was once thought to be a uniquely human trait but more recent work has revealed its presence in other vertebrates and in invertebrates. Insects have been shown to be lateralised in a variety of behaviours including forelimb reaching. The Hymenoptera (bees, wasps, ants) have emerged as a model system in which to study the evolution of lateralised behaviour because it contains species with a different grades of social organisation from solitary and eusocial that have evolved multiple times. This permits direct assessment of how conflict and co-operation among conspecifics contributes to the evolution of laterality. Previous studies have linked eusociality to the presence of population-level laterality but have ignored the presence of colonies in eusocial species such as bees and ants. Our game theoretic and Bayesian models predict that colony-level laterality should be present but also predict that such laterality will be weak, and that colonies in which all individuals were lateralised in the same direction would be punished because of predictability. By assessing the forelimb reaching movements of individual ants, we show that colony-level laterality does exist in the wood ant, Formica rufa, and is weak; colonies typically contain individuals with only a slight bias in forelimb use. Our findings explain why so many behaviours in social insects show relatively weak laterality and provide experimental evidence supporting colony-level laterality, which has previously been overlooked.

Jeremy E. Niven School of Life Sciences, University of Sussex, Falmer Brighton BN1 9QG, UK

14:00 *Filippo Abbondanza*

Handedness and neurodevelopmental disorders: a genetic approach

ABSTRACT. Filippo Abbondanza1, Silvia Paracchini1

The human brain appears symmetric, but the two hemispheres are functionally and structurally asymmetric. Handedness is the most accessible index of lateralization, and it partially reflects brain asymmetries. Worldwide, ~10% of individuals are left-handed, and an increase of non-right handedness frequency has been reported in neurodevelopmental conditions including dyslexia, schizophrenia and autism. These disorders are characterised, among others features, by atypical brain asymmetries. These findings highlight the potential of handedness to investigate brain structure and neurodevelopmental disorders.

Genetic studies of handedness have largely failed, with two exceptions. A first GWAS found an association between PCSK6, implicated in left-right body axes, and relative hand skills (pegboard test) in a dyslexia cohort. In the general population, genes involved in structural asymmetries and cytoskeleton dynamics were highlighted. A second GWAS in a large cohort identified four SNPs - in genes involved in microtubule growth, essential for cytoskeleton maturation - statistically associated with the categorical definition of handedness.

Building on these findings, this talk will address the effect of phenotypic measurements as well as follow up genetic studies. The relationship of different handedness/lateralisation indexes (including eye and leg preference) are investigated in large datasets (N~10,000). This analysis will inform genetic studies currently underway. In particular, a large meta-analysis of GWAS data for laterality measures is being conducted enriching the sample set with individuals presenting neurodevelopmental disorders. These data will contribute to our understanding of the role of asymmetries in neurodevelopment.

1: School of medicine, University of St Andrews, UK

14:20 *Barbara Fontana*

Behavioral laterality predicts fear avoidance responses but does not predict anxiety-related behavior in zebrafish (Danio rerio)

ABSTRACT. Introduction: Behavioral laterality is an evolutionarily conserved characteristic which is observed at populational level in humans. Zebrafish (Danio rerio) is an increasingly popular animal model in neuroscience due its high physiological homology to mammals. The objective of this study was to identify zebrafish with strong behavioral lateralization using an unconditioned y-maze protocol and evaluate if laterality bias played a role in conditioned fear response and anxiety-like phenotypes. Methods: 101 adult zebrafish were assessed in the y-maze for 1 hour. Behavioral lateralization was considered when an animal presented >60% bias for left or right turn. Following y-maze characterization, animals were pair housed for 24h and further tested on Pavlovian fear conditioning or novel tank diving task (NT), based on previously studies. Results: Zebrafish present robust behavioral lateralization in the y-maze (left-biased 27.18%, right-biased 27.18 % and non-biased 45.63%). Left ($p<0.001$) and right-bias ($p<0.005$) fish showed significantly more repetitions and lower number of alternations compared to the non-biased animals. In the conditioned fear test, fish that showed behavioral lateralization showed a significantly stronger avoidance response to a shock stimulus than non-biased animals ($p<0.05$). No significant bias effect was observed in the NT. Conclusions: Our data suggest that, in zebrafish, behavioral lateralization is related to different behavioral phenotypes in the y-maze and predicts performance on a conditioned fear test. Overall, our novel findings suggest that the y-maze test can be a valuable protocol to measure behavioral lateralization and could be used to further understand the evolutionary origins and functional relevance of left-right asymmetry.

14:40 *Maria Elena Miletto Petrazzini*

Fish as animal models to explore the relation between anatomical and functional asymmetries

ABSTRACT. Studies over the past few decades have shown that brain lateralization is not exclusive to humans but is rather widespread in animals. In recent years fish have become valuable models to address brain lateralization at different levels of complexity: from genes to behaviour. For instance, behavioural studies have shown that the advantages of having an asymmetric brain, such as the possibility of

processing multiple information in parallel, may be balanced by some disadvantages associated with poorer interhemispheric integration. However, the impact of brain lateralization on behaviour was not investigated leaving open the question of how these two aspects are linked. With respect to this issue, research on zebrafish has provided important insights into the relation between anatomical and functional asymmetries showing how altered brain lateralization affects behaviour.

ME Miletto Petrazzini1, M Dadda2

1School of Biological and Chemical Sciences, Queen Mary University of London, London, UK, 2 Department of General Psychology, University of Padova, Padova, Italy.

15:00 *Elena Lorenzi*

Spontaneous and light induced brain lateralization of c-Fos expression in the newly-hatched chick

ABSTRACT. Different forms of embryonic stimulation, such as temperature changes or acoustical experiences, induce long-lasting effects on the baseline level of c-Fos expression in different brain regions of domestic chicks (Gallus gallus). In the avian brain, thanks to the asymmetrical position in the egg determined by the Nodal cascade, embryonic light stimulation reaches selectively the left hemisphere (right-eye), inducing brain and behavioral asymmetries later in development. Here we investigated the role of embryonic light stimulation on the pattern of spontaneous c-Fos expression in different brain regions of the two hemispheres. We estimated c-Fos immunoreactivity in septum, intermediate medial mesopallium, hippocampus and preoptic area of the hypothalamus of chicks hatched from either dark-incubated or light-stimulated eggs. We found c-Fos expression to be asymmetrically modulated by light in a region-dependent fashion. Septum showed higher c-Fos expression in the left hemisphere only after embryonic light stimulation, whereas preoptic area showed a spontaneous right lateralization only in the absence of stimulation. Hippocampus and intermediate medial mesopallium did not show any significant lateralization nor any difference between the two conditions. Cell counting performed with DAPI staining revealed that differences found in c-Fos expression were not related to underlying differences in the overall cell densities. We thus confirmed the crucial role of environmental factors, such as light in embryo, on the development of brain lateralization,

showing that it also affects c-Fos expression. Interestingly, however, we provided evidence that some forms of brain asymmetries might be genetically predisposed or at least independent from the effect of light exposure.

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Funding Support: European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ Advanced Grant ERC PREMESOR G.A. [n_ 295517] to G Vallortigara

15:20 *Jadna Bogado-Lopes*

What is the role of new-neurons in the development of individual behaviour?

ABSTRACT. J Bogado-Lopes1,2, F Ehret1,2, AN Grzyb1,2, AE Rünker1,2, G Kempermann1,2

The interaction of individuals with their environment leads to the development of distinct behavioural patterns. Previously, we showed that isogenic mice kept in an enriched environment (ENR) established divergent and stable social and exploratory trajectories. Remarkably, the amount of exploratory activity, measured as roaming entropy (RE), correlated positively with adult hippocampal neurogenesis (AHN), a cellular plasticity mechanism in the hippocampus. We hypothesised that the feedback between activity (and hence experience of the environment) and brain plasticity, including AHN, is a core mechanism underlying brain individualization in ENR. To investigate whether disruption of AHN would compromise the exploratory activity and individualisation processes, we here used cyclin D2-ko mice with constitutively suppressed AHN (but normal hippocampal development), and their wild-type littermates (n = 40). Animals were housed together for 3-months in a novel large ENR enclosure consisting of 70 connected cages equipped with radio antennae for longitudinal tracking. Their cognitive performance was evaluated in the Morris Water Maze task (MWM) and AHN levels were assessed using BrdU labeling. We confirmed that the number of BrdU+ cells correlated with RE in the wild-type animals, and cyclinD2-ko mice had impaired performance in the reversal phase of MWM. Whereas wild-type animals developed stable exploratory trajectories, the behaviour of cyclinD2-ko mice remained more random. Furthermore, different patterns of correlations between exploratory

behavior, cognitive performance and AHN were observed in wild-type and knockout mice. Together, these results suggest that adult neurogenesis may have a crucial role at the individualisation of brain-related phenotypes.

1German Center for Neurodegenerative Diseases (DZNE) Dresden, 2Center for Regenerative Therapies TU Dresden (CRTD), Technische Universität Dresden, Dresden, Germany. Funding Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil.

15:30-17:30 Session 9: Poster Session

Poster Session I

Odd Number Posters

15:30 *Kristyn Borrelli*

P1 – Reward sensitivity in Hnrnph1+/- mice following acute methamphetamine administration as measured via intracranial self-stimulation

ABSTRACT. Kristyn N. Borrelli1, A. Carlezon Jr2, Elena H. Chartoff2, Camron D. Bryant1

1Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, Boston, MA; 2McLean Hospital, Department of Psychiatry, Harvard Medical School, Belmont, MA

Psychostimulant addiction is a heritable substance use disorder whose genetic basis is largely unknown. Several quantitative trait loci (QTL) in mice have been linked to addiction-related behaviors. The genes underlying these loci could provide clinical insight to the contribution of genetic factors in addictive disorders. We previously mapped and validated Hnrnph1 (heterogeneous nuclear ribonucleoprotein H1) as a quantitative trait gene underlying variance in methamphetamine (MA)-induced locomotor activity. Mice heterozygous for a frameshift deletion in coding exon IV of Hnrnph1 (Hnrnph1+/-) display decreased locomotor activity in response to MA compared to their wild-type littermates (Hnrnph1+/+). Microdialysis studies additionally show reduced MA-induced dopamine release in Hnrnph1+/- mice. We employed Intracranial self-stimulation (ICSS), an operant behavioral paradigm commonly used to assess shifts in sensitivity to stimulation of the dopaminergic mesolimbic reward circuit, to assess changes in ICSS responding following acute MA administration in

Hnrnph1+/- mice. Using stereotaxic surgery, we implanted a unilateral, stimulating electrode into the medial forebrain bundle (MFB). Activation of these fibers produces robust brain stimulation reward (BSR). Mice were trained on a fixed ratio 1 (FR1) schedule to receive MFB stimulation for each 1/4 turn of a response wheel. Increasing doses of MA were then administered every other day to detect MA-induced changes in BSR-associated reinforcement. We identified sex- and dose-dependent changes in the rate of ICSS responding in Hnrnph1+/- mice compared to wild-type littermates following acute MA administration. These findings support our previous work suggesting that Hnrnph1 dysfunction disrupts the rewarding properties of MA, further implicating this RNA binding protein in reward circuitry modulation.

15:30 *Anatoly Martynyuk*

P3 – Role of epigenetic mechanisms in intergenerational effects of anesthesia with sevoflurane in young adult rats

ABSTRACT. Each year millions of patients have surgeries under general anesthesia. Anesthetic exposure in early childhood or old age is linked to neurocognitive deficiencies. The adverse effects of anesthetics in young adults remain largely unexplored and there is practically no information on vulnerability of their future offspring. To investigate potential intergenerational effects of young adult anesthetic exposure, Sprague-Dawley postnatal day 56 rats (generation 1, G1) were anesthetized with 2.1% sevoflurane on 3 alternate days and mated 25 days later to produce offspring (G2). The G1 males and females had elevated systemic corticosterone, but only males had decreased hypothalamic cell surface K+-2Cl- (KCC2) Cl- exporter expression 1 h after the last sevoflurane exposure. Only G1 males exhibited persistent neurobehavioral deficiencies, exaggerated hypothalamic-pituitary-adrenal (HPA) axis responses to restraint, elevated levels of testosterone and reduced testis weight. Changes in hypothalamic-pituitary-testicular (HPT) axis functioning and expression of hypothalamic aromatase and estrogen receptors were consistent with a role for systemic testosterone/brain estradiol in G1 sex-specific effects of sevoflurane. Only the male offspring (G2) of exposed parents exhibited neurobehavioral deficiencies, but had unaltered HPA and HPT axis functioning. Finally, down-regulated Kcc2 expression in G1 and G2 male hypothalamus and hippocampus, and hyper-methylated Kcc2 promoter in G1 sperm and ovary and G2 male hypothalamus and

hippocampus support the involvement of epigenetic mechanisms in sevoflurane's intergenerational effects. Repeated exposure of young adult rats to sevoflurane results in sex-specific central and systemic abnormalities, some of which are passed to offspring, which could increase risk for disease later in life.

LS Ju1, JJ Yang1, N Xu1, J Li1, TE Morey1, N Gravenstein1,2, CN Seubert1, B Setlow2,3, and AE Martynyuk1,2

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Funding Support: Supported by the National Institutes of Health (R01NS091542 and R01NS091542-S to AEM), the Escher Autism Fund (AEM), the I. Heermann Anesthesia Foundation (LSJ), and the Jerome H. Modell, M.D., F.A.H.A. Endowed Professorship, Gainesville, Florida (NG).

15:30 *John Mootz*

P5 – The Role of Glutamate-related Proteins in Genetic Risk for High Methamphetamine Intake

ABSTRACT. The methamphetamine (MA) high drinking (MAHDR) and MA low drinking (MALDR) lines were selectively bred for voluntary MA consumption, and thus represent a model of differential genetic risk for MA intake. These lines differ in accumbal expression of a number of glutamate-related proteins. The MAHDR line expresses higher levels of the metabotropic glutamate receptor 5 (mGluR5) and the related scaffolding protein, Homer2a/b. Homer2a/b and mGluR5 have been implicated in intake and rewarding effects of other addictive drugs. There are no drugs that target Homer2a/b; however, there are drugs that target mGluR5, although they have never been tested in a model of high genetic risk for MA addiction, such as the MAHDR mice. Expression differences for glutamate-related proteins were found in one replicate of the MA drinking lines, and it is important to confirm these differences in an independent replicate. The nucleus accumbens from a separate replicate of MAHDR and MALDR lines was obtained and the same proteins analyzed. Expression of Homer2a/b was approximately 1.5x greater in MAHDR than MALDR mice, a difference nearly identical to the difference in the previous replicate. Results for mGluR5 are unclear at this time; however, when

two highly selective mGluR5 negative allosteric modulators were tested in MAHDR mice in which MA drinking had been established, neither significantly altered established MA intake levels. These results provide additional evidence of a role for Homer2a/b in MA intake, and suggest that mGluR5 may not be an effective treatment target for individuals with high genetic risk for MA addiction.

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15:30 *Karl Clark*

P7 – Light duration changes locomotor response dependence on HPA axis signaling

ABSTRACT. When vertebrates face acute stressors, their bodies rapidly undergo a repertoire of physiological and behavioral adaptations, which is termed the stress response (SR). These adaptations are mediated via the interaction of glucocorticoids and their cognate receptors following hypothalamic-pituitary-adrenal (HPA) axis activation. Rapid SR is observed within minutes of encountering a stressor and the rapid time domain rules out genomic responses that require gene expression changes. Using larval zebrafish, we showed that rapid locomotor response is elicited in acute light changes (acclimation in infrared (darkness)—1-min white light illumination—back to infrared) and that such response is dependent on mc2r (adrenocorticotropic hormone receptor) and nr3c1 (glucocorticoid receptor), but not on nr3c2 (mineralocorticoid receptor). However, when we tested larval zebrafish with 7.5-min light-dark repeat assays (7.5-min white light illumination—7.5 min infrared repeated four times), we found that both mc2r and nr3c1 homozygous mutants showed equivalent locomotor response to wild-type (WT) fish. This 7.5-min repeat assay is commonly used in the zebrafish community and described as eliciting stress- or anxiety-like behavior. Nonetheless, our results indicate that this locomotor response is not dependent on key HPA axis receptors (mc2r or nr3c1). Since stress is often operationally defined as increased HPA axis activity, we propose that this 7.5-min repeat assay should be more carefully characterized and defined before being reported as stress-like behavior. We want to further explore and understand how similar stimuli show altered dependence on HPA axis signaling for observed

locomotor responses based on changes in duration of the stimuli.

HB Lee, AN Sigafoos, and KJ Clark

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15:30 *Alfredo Ghezzi*

P9 – Molecular and neural mechanisms of alcohol-induced sleep disruption in Drosophila

ABSTRACT. Exposure to alcohol is known to trigger homeostatic adaptations in the brain that lead to the development of tolerance and dependence. These adaptations are also believed to be the root of a series of disturbances in sleep patterns that often manifest during the development of alcoholism and can have significant clinical and economic consequences. Unfortunately, the genetic pathways that control the effects of alcohol on sleep homeostasis are currently unknown, thus limiting our efforts to find effective treatment. Here, we report the use of Drosophila melanogaster as a biological model to understand the molecular underpinnings of the effects of alcohol on the neuronal substrates that control sleep. We show that in Drosophila, acute alcohol exposure causes disturbances in sleep patterns that resemble those described in mammals. These disturbances include an increase in total sleep duration, decrease sleep latency, as well as an increased number of sleep episode per day (fragmented sleep). Furthermore, we show that genes implicated in the neural adaptations behind alcohol tolerance, are also implicated in the regulation of sleep cycles. Manipulation of these alcohol responsive genes in the neuronal circuits involved in sleep/wake regulation in Drosophila significantly reduces the effects of alcohol on sleep patterns. Our results suggest that sleep and alcohol neuroadaptation share a common regulatory mechanism. We believe that the integration of genetic analyses with physiological modulation of neural activity within specific sleep circuits has tremendous potential to uncover the functionally relevant molecular targets whose action contributes to the deleterious effect of alcohol on sleep.

ME Ramirez-Roman1, A Anqueira-Gonzalez1, JL Agosto, A Ghezzi1 1Department of Biology, University of Puerto Rico, Rio Piedras; San Juan, PR 00931

15:30 *Gang Chen*

P11 – Transcriptomic analysis of differential treatment of Qi-dysregulation phenotypes revealed the participation of neuroengery in depression using Balb/cJ mouse strain

ABSTRACT. Stratified treatment by identification and treatment with specific antidepressants remain a challenge in the western medicine. Traditional Chinese Medicine (TCM) is a personalized medicine in which the diagnosis and treatment is based on identification of dysfunctional patterns, which may be shared by different diseases. The most prevalent TCM dysfunctional patterns in depression clinically include Qi stagnation, the repression of energy and Qi deficiency, the deficiency of energy. Previously we shown Balb/cJ mouse strain demonstrated both Qi-stagnation-like and Qi-deficiency-like phenotypes following chronic stress. Here, we found treatment with Qi-tonifying formula Sijunzi showed better efficacy than Qi-stagnation unblocking formula Yueju or regular antidepressant fluoxetine. Here, to further understand the genetic architecture underlying depression/antidepressant activity, we made transcritpomic sequencing and bioinformatic analysis of the prefrontal cortex, the crucial depression regulation region, on chronically-stressed mice, followed with these drug treatment. All three treatment groups showed different patterns of normalization of the gene expression perturbed by stress, with only 3 genes that were shared by three groups. Interestingly, two of the genes tkl2 and lct both process lactate, the important neuroenergenic molecule to maintain the normal function of the neurons. Furthermore, Sijunzi normalized additional lactate processing gene. Accumulating evidence suggests lactate and neuroengery were associated with depression, and depressive patients showed increased lactate concentration. We using unbiased systematic approaches, detected novel genes for lactate pathway implicated in depression pathogenesis, and potentially useful as the key target for treatment. This also suggests that the neural energy may serve as the common pathway underlying depression and supports the scientific connotation of the traditional medicine in treating depression.

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University of Chinese Medicine, Nanjing 210023, China; 2 Nanjing University of Chinese Medicine, Nanjing 210023, China 3 Interdisciplinary Institute for Personalized Medicine in Brain Disorders and Research Center for TCM Fang-Zheng, Jinan University, Guangzhou, 510632, China. 4 Co-innovation Center of Neuroregeneration, Nantong University, Nantong, Jiangsu 226001, China. Support: by the National Science Foundation of China (81874374) .

15:30 *Sumeyye Ozkaya*

P13 – Examining the Association Between Polygenic Risk Scores for Neuroticism and Extraversion, Cognitive Biases and Psychopathology Among Adolescents

ABSTRACT. Adolescence is a critical developmental period regarding individuals' mental health. Studies have shown that personality traits such as neuroticism, extraversion and cognitive biases are involved in the onset and maintenance of psychiatric disorders. While genetic variants have been shown to influence each of these factors, the extent to which they are caused by the same genetic factors remains unknown. We aimed to test potential associations between polygenic risk scores for neuroticism and extraversion obtained from the GPC (Genetics of Personality Consortium) and mental health and cognitive biases. To examine this, we used whole genome data and phenotypic data including psychological self-report measures (e.g. depression, anxiety) and performance on a range of attention, memory and interpretative bias tasks from 390 adolescents as part of the CogBIAS longitudinal study at Oxford University. Multilevel modelling across three time points revealed few associations between genetic risk for neuroticism and psychiatric disorders or cognitive biases. However, there were significant associations between extraversion and several of the anxiety subtypes as well as cognitive biases; most notably the memory bias. We also found evidence for time-by-genotype interactions for memory biases. These interactions suggested that those with a high polygenic score for extraversion develop an increasingly positive memory bias during adolescence. Our findings provide some potential causal pathways between genetic risk and protective factors and psychopathology, that if replicated, may represent novel targets for prevention and intervention.

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15:30 *Anna Holubova*

P15 – Different social behavior and oxytocin responses to acute methamphetamine treatment in juvenile female rats perinatally exposed to stress and/or drug administration

ABSTRACT. Methamphetamine (MA) is an addictive psychostimulant, often abused by drug addicted women during pregnancy. The offspring of drug-addicted mothers are often exposed to perinatal stressors. The present study examines the effect of perinatal stressors and drug exposure on plasma oxytocin (OXY) levels and social behavior in female progeny. Rat mothers were divided into three groups according to drug treatment during pregnancy: intact controls (C); saline (SA, s.c., 1 ml/kg); MA (s.c., 5 mg/kg). Litters were divided into four groups according to postnatal stressors lasting from PD1 to 21: non-stressed controls; maternal separation; maternal cold-water stress; maternal separation plus cold-water stress. On postnatal day 30, acute MA or SA were administrated and female progeny was exposed to Social play test lasting 15 minutes. Immediately after Social play test, the rats were sacrificed. Trunk blood was collected and plasma OXY was measured by specific ELISA after extraction. Our results showed that acute MA administration changes the social play and social exploration differently. Acute MA also significantly increases plasma OXY levels in juvenile female rats; this effect was observed in prenatally intact rats only. Prenatal exposure of rats to mild stressor of daily SA injection prevented both acute MA induced OXY stimulation and also stress induced OXY inhibition. Although postnatal MA and stress exposure exert opposite effects on OXY release in juvenile rats, our data point out the modulatory role of prenatal mild stress in OXY response to postnatal stressors or MA treatment.

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1Department of Physiology, Third Faculty of Medicine, Charles University, Prague, Czech Republic Funding support: PROGRES Q 35, GAUK 850317, 260388/SVV/2019 from Charles University, 18-09296S from the Grant Agency of the Czech Republic, PharmaBrain

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15:30 *Stephen Boehm*

P17 – Early-life low-level chronic lead (Pb) exposure alters anxiety-like behavior, but not alcohol intake, in adult C57BL/6J mice

ABSTRACT. Human association studies have found that childhood lead (Pb) exposure is highly correlated with substance use disorder (SUD) in adulthood. Since 2012, the average blood Pb levels (BLL) found among children in lower socioeconomic income environments has generally ranged from 3-5 mg/dL. Although historically lower, these Pb exposure levels may still be sufficient to alter brain and behavior. Here we sought to model such low-level Pb exposure in mice. At weaning (PND 21) C57BL/6J mice were assigned to three-week Pb (30 or 0 ppm) exposure via the drinking water resulting in BLL of 6.6±0.5 and 5.1±0.4 mg/dl in males and females, respectively. Once mice reached adulthood (PND 70±5) they were tested for anxiety- (elevated plus maze) and depressive-(forced swim) like behavior, and then given access to alcohol (20% v/v) for 2hrs per day for three weeks. We hypothesized that mice with early-life low-level Pb exposure would exhibit heightened anxiety- and depressive-like behavior, and consume more alcohol, than their non-Pb exposed counterparts. Early data suggest that although Pb exposure does not alter immobility latency or time in the forced swim task, or limited-access alcohol intake, it significantly decreases open arm entries on the elevated plus maze ($p<0.05$), suggesting that early-life low-level Pb exposure increases anxiety-like behavior. These results suggest that low-level childhood exposure to Pb may alter the developing brain sufficiently to produce adult changes in overall anxiety, but not necessarily propensity to consume alcohol.

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15:30 *Nicole Tay*

P19 – Longitudinal DNA methylation changes related to reinforcement psychopathology in adolescence

ABSTRACT. In recent years, much interest has been focused on epigenetic mechanisms underlying environmental influences related to the development of behaviour and psychopathology. In particular, DNA methylation, one of the key epigenetic processes, has been the central topic of mental health research. While DNA methylation has been associated with environmental influences and the development of psychiatric illnesses, longitudinal methylation changes have not been well described. Current analyses of DNA methylation variations over time have mostly been related to age-related changes. With the advantage of having access to the longitudinal adolescent IMAGEN cohort, our aim is to identify novel DNA methylation patterns over time and relate them to neurobehavioural features and development of psychopathologies. Here I will present our preliminary findings on dynamic changes in methylation patterns identified within the IMAGEN cohort. I will also describe how these dynamic methylation patterns observed relate to environmental influences and neurobehavioural features.

Nicole Tay1, Yan Sun1, Tianye Jia1,2,3, Yun Liu4, Alex Ing1, Zuo Zhang1, Riya Paul5, Bertram Mueller-Myhsok5, Gunter Schumann1

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15:30 *Yuriy Slyvka*

P21 – Forced swim test and CB-1 receptor expression in hippocampus of offspring of obese male mice

ABSTRACT. Offspring of obese male mice demonstrate impaired metabolism, obesity, and changes of behaviour. We performed a forced

swim test (FST) and detected the expression of type 1 endocanabioid receptor (CB1-R) in hippocampus to understand the stress coping strategy to an acute inescapable stress in such animals. Methods: Male C57Bl6/N mice were placed for 12 weeks on either a high fat diet (HFD, 45% kcal fat) to induce obesity or a normal fat diet (LFD, 10% kcal fat) and then mated with females on LFD. Offspring of both parents on LFD formed Group 1 and offspring of males on HFD and females on LFD formed Group 2. Pups were fed regular chow and tested at 1.5 and 6 months. The FST was performed and CB-1R expression was detected in different regions of hippocampus by immunohistochemistry staining. Results: Analysis of FST has shown that all 1.5 month offspring from Groups 1 an 2 demonstrated more “struggling” behaviour than at 6 months. At 1.5 months male offspring from Group 2 demonstrated less “struggling” behaviour than Group 1 male offspring. At 6 months female offspring of Group 2 swam more and floated less than females of Group 1 or the animals of the same group at 1.5 months. Direct parallelism between the results of FST and expression of CB-1R in different regions of hippocampus were not observed. Conclusion: Paternal HFD results in offspring with changed results of FST that are not related to the expression of CB-1R in hippocampus.

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15:30 *Rupert Overall*

P23 – The Adult Neurogenesis Map

ABSTRACT. The hippocampus is a key brain structure for learning and memory. It not only processes input from the environment, but also fundamentally influences behaviour. This means that the neural network in the hippocampus is a core part of an information loop connecting environmental stimulus and response. It is particularly intriguing that this special brain region is also home to a population of neural stem cells which allow the environmentally-regulated creation of new neurons, throughout the life of the organism, that add an extra level of flexibility to hippocampal performance. We have previously shown that the regulation of the stem cell pool and the generation of new neurons are under complex genetic control. We also maintain a structured database of all genes reported to affect adult hippocampal neurogenesis in some

way. We are now extending this effort to encompass behavioural phenotypes and environmental stimuli. The resulting information is being organised into a structured SBML map to enable interactive browsing and complex searching of the knowledgebase, as well as to provide a platform for predictive modelling. We present here an outline and working draft of the Adult Neurogenesis Map and look forward to community feedback as the project expands.

RW Overall1

1German Center for Neurodegenerative Diseases (DZNE), Dresden, Germany

15:30 *Jee-Yin Ahn*

P25 – The role of ErbB3 binding protein 1 (EBP1) in brain development and gene silencing control in mice

ABSTRACT. ErbB3-binding protein 1 (EBP1) is a well-conserved DNA/RNA-binding protein that is implicated in cell growth, apoptosis, and differentiation. . To define the physiological function of EBP1 in vivo, we generated Ebp1-mutant mice that showed loss of Ebp1 expression. Here, we report that EBP1 is essential for embryonic development including and regulation of transcriptional repression. Loss of Ebp1 in mice results in aberrant organogeneses, including malformation of the brain and death between E13.5 and 15.5 owing to severe hemorrhages, with massive cell death and cessation of cell proliferation. Consistently, mice lacking EBP1 in the central nervous system [Nestin-Cre; Ebp1flox/flox] showed developmental defects of the brain, with substantial neuron loss. Importantly, the Ebp1(-/-) mice demonstrated upregulation of Suv39H1-dependent histone H3 lysine 9 (H3K9) trimethylation and subsequent activation of DNMT1, displaying markedly increased global DNA methylation. Moreover, EBP1 suppressed the transcriptional expression of Dnmt1 by altering the recruitment of RNA polymerase II at its promoter region and also interrupted DNMT1 binding at its target gene, at the survivin promoter region. Our finding uncovers a key role of EBP1 in embryonic development and as a potent co-regulator of gene expression that might coordinate epigenetic modification.

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University School of Medicine, Suwon 16419, Korea Funding Support: A grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI17C0227

15:30 *Callum Dark*

P27 – Functional characterisation of ADHD-associated gene variants using the zebrafish as an animal model

ABSTRACT. Attention deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder of childhood, affecting around 5% of children worldwide. Individuals are typically diagnosed with high levels of activity, inattention, and impulsivity, which have strong negative impacts on their academic and interpersonal development. Despite research into the genetic background of ADHD uncovering several associated genes, the functional validation of these genes is lacking. To address this, we have investigated the function of two ADHD associated genes to determine their roles in this disorder. These genes are CHMP7, a gene predicted to be functionally relevant to ADHD, and DUSP6, one of the first significant ADHD genome wide association hits. This led us to generate zebrafish mutant lines for chmp7 and dusp6 to examine how variants in these genes contribute to the ADHD phenotype. Individuals homozygous for the ADHD associated variant in CHMP7 have a 33% reduction in CHMP7 transcript. Therefore we investigated activity in heterozygous fish, and demonstrate significantly increased activity compared to their siblings. Similarly, we have examined fish mutants for dusp6 and identified significant increases in activity in homozygous mutant fish compared to siblings. Together these provide the first examples of functional validation for ADHD associated variants from genome wide association studies or functional prediction pathways, and provide insight into the potential mechanisms underlying the ADHD phenotype. I will present functional data confirming the relevance of these genes in the development of ADHD, as well as data exploring the mechanisms underlying their roles in the disorder.

Callum Dark1, Caitlin Williams, Dr Ziarih Hawi2, Dr Janette Tong2, Prof Mark Bellgrove2 and Dr Robert Bryson-Richardson1

1 School of Biological Sciences, 2 School of Psychological Sciences; Monash University, Melbourne, Australia

15:30 *Stephanie Kelly*

P29 – Natural polymorphism in protein kinase G modulates functional senescence in D. melanogaster

ABSTRACT. The common fruit fly, Drosophila melanogaster, is a well characterized model for neurological disorders and is widely used to investigate the biology of aging, stress tolerance and pleiotropy. The foraging (for) gene encodes a cGMP-dependent protein kinase (PKG), which has been implicated in several behavioral phenotypes including feeding, sleep, learning and memory, and environmental stress tolerance. We used the well-established Drosophila activity monitor (DAM) to investigate the effects of the conserved NO/cGMP/PKG signaling pathway on functional senescence. Our results show that the polymorphic for gene confers protection during low oxygen stress at the expense of longevity and a decline in locomotor activity with age in D. melanogaster, which suggests a novel role for the PKG pathway in healthy aging and senescence.

Stephanie P. Kelly and Ken Dawson-Scully*
Florida Atlantic University, Department of Biological Sciences, Boca Raton, FL, 33431

15:30 *H Rawsthorne*

P31 Using C. elegans social behaviour to investigate genes associated with autism spectrum disorder

ABSTRACT. Autism spectrum disorder (ASD) is characterised by a triad of impairments, one of which is impaired social behaviour. Several different gene mutations are implicated in ASD however it is not clear how these result in behavioural impairment. C. elegans provides a tractable system to investigate the impact of genetic variants on cellular function and relate this to neural circuits that co-ordinate behaviour. We have shown that C. elegans adults elicit a social behaviour in response to progeny1. Using this paradigm, we can probe how genetic variants impact the function of neural circuits that underpin social behaviour. Neuroligin is a synaptic adhesion protein which aids synaptic function. Genetic variations in neuroligin have been shown to be highly penetrant in ASD. The C. elegans genome encodes a single neuroligin orthologue, nlg-1. The nlg-1(ok259) allele is a functional null and has been used in this study to investigate the role of neuroligin in co-ordinating progeny dependent social behaviour. We have identified that nlg-1(ok259) adult worms have an impaired social behaviour in response to progeny.

To further our investigations, we have used CRISPR/Cas9 to edit the C. elegans genome to contain an arginine to cysteine amino acid substitution identified in individuals with ASD. In this way we hope to provide further insight into how genetic variations in neuroligin impact on the function of neuronal circuits to cause the behavioural impairments diagnosed in ASD.

Helena Rawsthorne, Umaymah El Ghiffari Barnett, Evie Goss-Sampson, Fernando Calahorro, James Dillon, Vincent O'Connor, Lindy Holden-Dye

1. Scott, E. et al. An oxytocin-dependent social interaction between larvae and adult C. elegans. Sci Rep 7, 10122 (2017). Biological Sciences, University of Southampton, SO17 1BJ. Funding support: The Gerald Kerkut Charitable Trust

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GBB 2019: GENES, BRAIN AND BEHAVIOR 2019

PROGRAM FOR SUNDAY, MAY 12TH

Days: previous day next day all days

View: session overview talk overview

08:30-09:00 Session 10: Registration

Registration

09:00-11:00 Session 11: Symposium 3

Genes-environment interactions in brain and behavior

CHAIR: *Amy Dunn*

09:00 *David Mets*

Learning is enhanced by tailoring instruction to individual genetic differences

ABSTRACT. It is widely argued that personalized instruction based on individual differences in learning styles or genetic predispositions could improve learning outcomes. However, this proposition has resisted clear demonstration in human studies, where it is difficult to control experience and quantify outcomes. Here, we take advantage of the tractable nature of vocal learning in songbirds (Lonchura striata domestica) to test the idea that matching instruction to individual genetic predispositions can enhance learning. We use both cross-fostering and computerized instruction with synthetic songs to demonstrate that matching the tutor song to individual predispositions can improve learning across genetic backgrounds. Moreover, we find that optimizing instruction in this fashion can equalize learning differences across individuals that might otherwise be construed as fixed and genetically determined. Our results demonstrate potent, synergistic interactions between experience and genetics in shaping song, and indicate the likely importance of such interactions for other complex learned behaviors.

David G. Mets1 and Michael S. Brainard1,2 1 Center for Integrative Neuroscience, University of California, San Francisco, CA 94158; Howard Hughes Medical Institute, University of California, San Francisco, CA 94158. 2Departments of Physiology and Psychiatry, University of California, San Francisco, CA 94158.

09:30 *Michael Saul*

Individual differences govern cocaine-related neurobehavioral phenotypes

ABSTRACT. Addiction vulnerability is highly heritable and addiction behaviors differ between sexes. Addiction studies in non-human animals should account for these known biological sources of variation, yet addiction phenotypes in mice are often studied in a single sex and strain. Here, we test how the behavioral and neural transcriptional response to cocaine depends on both genetic diversity and sex among genetically diverse mice. Comparing the eight founder strains of the Diversity Outbred population, we found robust differences in cocaine intravenous self-administration – especially among wild-derived strains. Using RNA sequencing of striatum from the eight founder strains of the Diversity Outbred, we assessed the main effects of repeated cocaine versus saline injection, genetic background, sex, and all interaction effects on global gene expression. Most effects were genetic – transcriptional profile is more highly heritable than in the BXD – but few genes were differentially expressed through a main effect of cocaine. Instead, cocaine-related molecular phenotypes manifested as interactions with sex and genetic background, and the strongest cocaine exposure effects were attributable to cocaine's interaction with both sex and genetic background. A number of genes were upregulated after cocaine exposure in a sex and strain specific manner including the immediate early gene Arc and the cytoskeletal adapter to PI3K signaling Myo16. Altogether, these results demonstrate the context specificity of cocaine response mechanisms while reiterating the necessity of incorporating genetic diversity and sex differences when studying the biological basis of addiction. The variation in neurobehavioral response to cocaine suggests potential mechanisms of differential vulnerability to addiction.

Michael C. Saul1, Price E. Dickson1, Vivek M. Philip1, Leona H. Gagnon1, Tyler Roy1, Troy Wilcox1, Michael Leonardo1, Ashley Olsen1, Center for Systems Neurogenetics of Addiction1,2,3,4, Elissa J. Chesler1. Funding Support: NIDA P50 DA039841, NIDA R01 DA037927. 1The Jackson Laboratory, Bar Harbor, ME; 2UNC Chapel Hill, Chapel Hill, NC; 3SUNY Binghamton, Binghamton, NY; 4Pittsburgh University, Pittsburgh, PA

10:00 *Danila Cuomo*

Using a population-based mouse model for assessment of neurotoxicity in response to early-life lead exposure

ABSTRACT. Danila Cuomo1, Megan Nitcher1 and David Threadgill1

Most human diseases result from a complex interplay of genetic, epigenetic and environmental factors, and current scientific approaches do not adequately capture these complex interactions. Understanding such gene-by-environment interactions will enable a more accurate toxicant risk assessment and public health protection. Traditional epidemiological approaches are limited in exploring factors contributing to differential susceptibility. To overcome this limitation, new genetically-diverse mouse resources such as the Collaborative Cross and Diversity Outcross have been developed to better model the genetic diversity found in human populations. Childhood exposure to lead, a potent neurotoxin for which there is no safe blood level, can impact intelligence and behavior. To specifically address the influence of genetic background on neurotoxicity from lead exposure, we are utilizing a recombinant inbred intercross mouse population which allows controlled exposures within a population setting to identify genetic polymorphisms that drive either susceptibility or resistance to lead neurotoxicity. To this end, F1 males and females derived from crosses of Collaborative Cross inbred lines receive early-life exposure to lead through lactation and then through drinking water to mimic human exposure. Preliminary results reveal significant variation in blood lead levels between strains exposed to the same dose. We are also assessing long-term effects of lead exposure on behavior and cognition in adult mice with early-life exposure. Differences between strains could provide us the key in understanding mechanisms by which genetics and toxic exposure contribute to neurological phenotype and provide new tools for exposure detection, risk assessment, and interventions to reduce lasting effects of early-life lead exposure.

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10:30 *Byron Jones*

Gene-Environment Interactions in Neurotoxicology Research

ABSTRACT. Exposure to environment toxicants including pesticides, particulate matter from

engine exhaust and other forms of smoke take a toll on human health. Depending on the toxicant however, not all individuals are equally susceptible to the deleterious effects. In assessing relative risk across individuals, genetic constitutions come in play. For example, it has been shown that risk for developing Parkinson's disease following exposure to paraquat, an herbicide, is markedly affected by one's genotype for the Glutathione S-transferase enzyme. More robust research on toxicogenetics requires an appropriate animal model. In this presentation, the author will present his work on genetic variability in neurological response to paraquat, MPTP and an organophosphorus compound, diisopropylflurophosphate in the BXD family of recombinant inbred mouse strains.

Byron C. Jones, University of Tennessee Health Science Center, Memphis TN Supported in part by USPHS grant ES 022614 and DoD grant W81XWH-17-1-0472.

11:00 *Amy Dunn*

Gene-by-diet regulation of Alzheimer's disease pathogenesis

ABSTRACT. AR Dunn1, AR Ouellette1, SM Neuner1,2, J-G Zhang1, V Philip1, KMS O'Connell1, CC Kaczorowski1 Alzheimer's disease (AD) is complex, with both genetic and environmental factors regulating disease progression. Identification of gene-by-environment interactions that modulate AD pathogenesis will be critical to understanding disease mechanisms and developing novel and personalized treatments; however, gene-by-environment interactions in AD have been largely under-explored. We recently developed a panel of genetically diverse mice carrying familial AD mutations (AD-BXDs; Neuner, 2018) that are ideally suited to investigate translationally-relevant GxE interactions. Here, we used AD-BXDs to determine how genetics and diet interact to modify AD-related pathogenesis. We fed a chronic high-fat diet (HFD; 45% fat) to 10 strains of AD-BXDs and nontransgenic littermates (Ntg-BXDs) and monitored metabolic and cognitive function. Finally, we analyzed gene expression in the hippocampus and hypothalamus using RNAseq. Gene-by-diet interactions accounted for a substantial proportion of variance in metabolic and cognitive phenotypes across the population, and the contribution of gene-by-diet interactions on these phenotypes differed depending on genotype. Metabolic function correlated more closely with cognitive function in AD-BXDs compared to Ntg-BXDs. These results suggest

that diet and genetic background interact to mediate vulnerability to AD pathogenesis, and that metabolic factors (e.g., weight, glucose metabolism) contribute to cognitive decline differentially in normal aging versus AD. Ongoing analyses will determine how transcriptomic changes within the hippocampus and hypothalamus regulate effects on cognitive and metabolic phenotypes in chow- and HFD-fed mice. Identifying genetic modifiers of environmental contributors to AD will be critical to improvements in personalized therapeutics and precision medicine to delay, prevent or treat the disease.

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11:00-11:30 Coffee Break

11:30-12:30 Session 12: Young Investigator Award

Young Investigator Award

Dr. Zoe Donaldson

CHAIR: *Richard Radcliffe*

11:30 *Zoe Donaldson*

Functional variation in neuromodulatory genes as a source of behavioral diversity

ABSTRACT. Evolutionarily ancient neuromodulatory systems play an important role in mood and behavior. Variation in these systems is thought to contribute to inter- and intra-species behavioral diversity and differences in susceptibility to mental illness in humans. In order to elucidate the contribution of genetic variation in neuromodulatory genes to behavioral diversity, I have focused on two candidate genes: the vasopressin V1a receptor, which plays a major role in social behavior, and the serotonin 1a receptor, which modulates anxiety and stress-related behaviors. Variation in repetitive elements in the promoter of the V1a receptor gene have been associated with both individual and species level differences in receptor expression and social behavior in voles. I demonstrated that these variants directly contribute to differences in gene expression and behavior by creating transgenic mice carrying different versions of this repetitive element. The highly mutable nature of repetitive DNA elements may thus represent an evolutionary mechanism for generating sociobehavioral diversity. Within the serotonin 1a

receptor system, a single nucleotide polymorphism (SNP; rs6295) in the gene promoter has been linked to differences both in depression risk and anti-depressant responsiveness in humans. Using a combination of epidemiological and post-mortem approaches in humans, I found that rs6295 has region-specific and developmental impacts on gene expression and is associated with increased risk for psychiatric hospitalization. I then created multiple humanized lines to model rs6295, which demonstrated the importance of epistatic interactions and genomic location in SNP penetrance and highlighted the challenges associated with modeling non-coding human genetic variation in mice.

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Current Funding Support: Whitehall Foundation, Dana Foundation, NSF IOS-1827790, NIH DP2OD026143, R00 MH102352

12:30-13:30 Lunch Break

13:30-15:30 Session 13: Selected Talks 1

Themed Talks

Mood, Social interactions, cognition and learning.

CHAIRS: *Gang Chen* and *Karl Clark*

13:30 *Noam Meiri*

Early-life heat exposure influence resilience or vulnerability to heat stress later in life by an epigenetic mechanism

ABSTRACT. Stressful events in early life might lead to stress resilience or vulnerability, depending on an adjustable stress-response set-point, which can be altered during postnatal sensory development and involves epigenetic regulation of corticotropin-releasing hormone (CRH). During the critical developmental period (CDP) of thermal-control establishment in 3-day-old chicks, heat stress was found to affect both body temperature and expression of CRH in the hypothalamic paraventricular nucleus (PVN). Both increased during heat challenge in chicks that were trained to be vulnerable to heat, whereas they decreased in chicks that were trained to be resilient. Accordingly, DNA CpG methylation (5mC) and hydroxymethylation (5hmC) at the CRH intron, which we found to serve as a repressor element, displayed low

5mc% alongside high 5hmc% in resilient chicks, and high 5mc% with low 5hmc% in vulnerable ones. RE1-silencing transcription factor (REST), which has a binding site on this intron, bound abundantly during acute heat stress and was nearly absent during moderate stress, restricting repression by the repressor element, and thus activating CRH gene transcription. Furthermore, REST assembled into a protein complex with TET3, which bound directly to the CRH gene. Finally, the adjacent histone recruited the histone acetylation enzyme GCN5 to this complex, which increased H3K27 acetylation during harsh, but not moderate heat conditioning. We conclude that an epigenetic mechanism involving both post-translational histone modification and DNA methylation in a regulatory segment of CRH is involved in determining a resilient or vulnerable response to stress later in life.

N Meiri 1, T Cramer 1,2, T Rosenberg 1,2, T Kisliouk 1

1Institute of Animal Science, ARO, The Volcani Center, Bet Dagan, Israel, 2The Robert H. Smith Faculty of Agriculture, Food and Environment, the Hebrew University of Jerusalem, Rehovot, Israel, Funding Support: Israel Science Foundation grant no. 1646/15

13:45 *Hee-Sup Shin*

The superior colliculus-mediodorsal thalamus-basolateral amygdala circuit underlies the psychotherapeutic regimen for fear disorders

ABSTRACT. We have previously shown that the mediodorsal thalamic nucleus (MD) is critically involved in modulation of fear memory. Now we have identified the neural circuits upstream and downstream of this MD function, and showed that this circuit underlies the psychotherapy for long lasting attenuation of fear memory. A psychotherapeutic regimen utilizing alternating bilateral sensory stimulation (ABS), also called eye movement desensitization and reprocessing (EMDR), has been used to treat posttraumatic stress disorders (PTSD). However, the neural basis underlying the long-lasting effect of this treatment, has not been identified. Here, we found a novel neuronal pathway mediating the persistent fear attenuation driven by the superior colliculus (SC) activity. We successfully induced a long-lasting fear reduction in fear-conditioned mice by pairing visual ABS with conditioned tone stimuli during fear extinction. Among the visual stimulation protocols tested, the ABS-pairing provided the strongest fear-reducing effect and

yielded sustained increases in the activities of the SC and the MD. Optogenetic manipulations revealed that the SC-MD circuit was necessary and sufficient to prevent the return of fear. The ABS suppressed fear-encoding cells and stabilized inhibitory neurotransmission in the basolateral amygdala (BLA) through an MD-BLA feedforward inhibitory circuit. Taken together, these results revealed the SC-MD-BLA circuit underlying an effective strategy for sustainably attenuating traumatic memories in PTSD patients.

Hee-Sup Shin Center for Cognition and Sociality
Institute for Basic Science

14:00 *Marie Mennesson*

Kainate receptor auxiliary subunit NETO2 modulates maturity and excitability of amygdala

ABSTRACT. NETO2 is an auxiliary subunit for kainate receptors. We previously demonstrated that Neto2 knockout (KO) mice have increased fear expression and slower extinction in cued fear conditioning. Neto2 is widely expressed in the amygdala, medial prefrontal cortex, and ventral hippocampus, brain regions that form the central fear circuit. To find the cellular mechanisms associated with the fear phenotype, we measured the number of parvalbumin (PV)-expressing interneurons surrounded by perineuronal nets (PNNs), since their amount increases throughout development and they are required for fear memory consolidation. In amygdala the fraction of PV-PNN positive cells within the total PNN population was smaller ($p=0.003$) and PV staining intensity was lower ($p=0.002$) in Neto2 KO mice compared to WTs, suggesting an immature state of the Neto2-/- amygdala. In the basolateral amygdala, Neto2 KO mice had higher amplitude and frequency of action-potential independent glutamatergic events (mEPSCs) compared to WT mice, indicating stronger glutamatergic synapses, but there was no differences in spontaneous glutamatergic and GABAergic currents. We also observed a larger density of spines on thin dendrites of Neto2 KO compared to WT mice. After fear acquisition Neto2-/- mice had a higher number of c-Fos positive cells in the amygdala compared to Neto2+/+ mice. In conclusion, our results suggest that NETO2 is important for maturity and excitability of the amygdala, potentially influencing fear expression and extinction during cued fear conditioning in adult mice.

Marie Mennesson1, 2, Ester Orav1,3, Adrien Gigliotta1, 2, Natalia Kulesskaya1, Suvi Saarnio1, Anna Kirjavainen1, Sebnem Kesaf1, 3 , Frederike Winkel3, Maria Llach Pou3, Juzoh Umemori3, Vootele Voikar3, Victoria Risbrough4, Juha Partanen1, Eero Castrén3, Sari Lauri1,3, Iiris Hovatta1,2

1 Molecular and Integrative Biosciences Research Program, University of Helsinki, Finland ; 2 Department of Psychology and Logopedics, Medicum, University of Helsinki, Finland ; 3 Neuroscience Center, University of Helsinki, Finland ; 4 Department of Psychiatry, University of California, San Diego, USA

14:15 *Helena Rawsthorne*

Using C. elegans social behaviour to investigate genes associated with autism spectrum disorder

ABSTRACT. Autism spectrum disorder (ASD) is characterised by a triad of impairments, one of which is impaired social behaviour. Several different gene mutations are implicated in ASD however it is not clear how these result in behavioural impairment. C. elegans provides a tractable system to investigate the impact of genetic variants on cellular function and relate this to neural circuits that co-ordinate behaviour. We have shown that C. elegans adults elicit a social behaviour in response to progeny1. Using this paradigm, we can probe how genetic variants impact the function of neural circuits that underpin social behaviour. Neuroligin is a synaptic adhesion protein which aids synaptic function. Genetic variations in neuroligin have been shown to be highly penetrant in ASD. The C. elegans genome encodes a single neuroligin orthologue, nlg-1. The nlg-1(ok259) allele is a functional null and has been used in this study to investigate the role of neuroligin in co-ordinating progeny dependent social behaviour. We have identified that nlg-1(ok259) adult worms have an impaired social behaviour in response to progeny. To further our investigations, we have used CRISPR/Cas9 to edit the C. elegans genome to contain an arginine to cysteine amino acid substitution identified in individuals with ASD. In this way we hope to provide further insight into how genetic variations in neuroligin impact on the function of neuronal circuits to cause the behavioural impairments diagnosed in ASD.

Helena Rawsthorne, Umaymah El Ghiffari Barnett, Evie Goss-Sampson, Fernando Calahorro, James Dillon, Vincent O’Connor, Lindy Holden-Dye

1. Scott, E. et al. An oxytocin-dependent social interaction between larvae and adult C. elegans. Sci Rep 7, 10122 (2017). Biological Sciences, University of Southampton, SO17 1BJ. Funding support: The Gerald Kerkut Charitable Trust

14:30 *Yehuda Ben-Shahar*

Modeling WBS-related gene dosage effects on neuronal and social traits in Drosophila

ABSTRACT. Haploinsufficiency due to a hemideletion in the human chromosome 7q11.23 region is associated with the Williams-Beuren Syndrome (WBS), a developmental disorder characterized by stereotypically hypersocial personality and cardiovascular pathologies. Although the WBS leads to hemizygosity of just 28 protein coding genes, which specific gene(s) contributes to the dramatic social phenotype observed in affected individuals remains mostly unknown. Because majority of the protein-coding genes affected by the typical WBS deletion have orthologs in the fly genome, we developed a research program that aims to take advantage of the power of Drosophila in vivo genetics to decipher the molecular, cellular, and developmental processes that might be affected by WBS genes in the nervous system, and how they affect conserved neural substrates that drive animal sociality. By using a neuronal-specific RNAi-dependent gene knockdown screen of WBS-related genes in Drosophila, we demonstrate that reducing the dosage of at least one gene, eIF4H1, an ancillary modulatory subunit of the highly conserved, rate-limiting eIF4F eukaryotic translation initiation complex, leads to abnormal social interactions in Drosophila. Because recent studies have suggested that the translation initiation complex plays a role in neuronal and behavioral plasticity at the developmental and physiological timescales, including pathologies associated with autism and intellectual disabilities, these data suggest that gene dosage of the human eIF4H1 locus may be responsible, at least in part, to some of the observed characteristic social phenotypes expressed by WBS individuals.

Iris Chin1, Cassondra Vernier1, Yehuda Ben-Shahar1

1Department of Biology, Washington University in St. Louis, St. Louis, MO, USA. Funding Support: National Institute of Health (USA), NIEHS R01 ES02599; National Science Foundation (USA), IOS1707221, DBI1707221.

14:45 *Laura Molina-Garcia*

Neuropeptide modulation of aversion and reward during learning

ABSTRACT. When an animal repeatedly encounters a signal coupled with either a punishment or a reward, it eventually learns to expect both to occur together in a process called associative learning. A central goal in neuroscience is to understand how neural circuits integrate conflicting (rewarding and aversive) experiences that need to be behaviourally resolved during learning.

To shed light into this process at the molecular and cellular level, we are dissecting a neural circuit for sexual conditioning in the C. elegans male.

Sexual conditioning is a form of male-specific associative learning by which a rewarding experience with mates overrides an aversive association with starvation, thus switching the males' behaviour to a stimulus from repulsion to attraction (Sakai et al., 2013). Previously, our lab implicated the Mystery Cells of the male (MCMs) interneurons and the neuropeptide PDF-1 as regulators of the sexually conditioned switch (Sammut et al., 2015).

Here we show a dual role for the neuropeptide PDF-1 in the regulation of both aversive and appetitive learning in C. elegans. By using a Cre-Lox intersectional strategy we find that PDF acts in distinct subsets of neurons to promote reward and to promote aversion. Also the molecular mechanisms underlying aversion and reward seem to be distinct: whereas only PDF-1 is required to signal reward, both PDF-1 and PDF-2 act redundantly to promote aversion. A similar dual role in encoding value has been recently described for dopamine in both mice and flies, suggesting a conserved value-assignment logic in neural circuits across evolution.

Laura Molina-Garcia1, Susana Colinas-Fischer1, Sergio Benavides-Laconcha1, Lucy Lin1 & Arantza Barrios1

1Department of Cell and Developmental Biology. University College London. UK

15:00 *Roshan Jain*

A forward genetic screen reveals the calcium-sensing GPCR CaSR as a novel modulator of larval sensorimotor decision-making

ABSTRACT. Animals respond to their changing environment through decision-making: selecting

one behavioral response from a set of alternatives expected to produce different outcomes. We have developed a simple decision-making paradigm in larval zebrafish using the evolutionarily conserved acoustic startle response. Larvae select between two distinct behaviors to respond to sudden acoustic stimuli: a Short-Latency C- bend (SLC) or a less vigorous Long-Latency C-bend (LLC), which differ in their kinematic, neuronal, and genetic requirements. This sensorimotor choice is dynamically modulated by stimulus quality and history, as well as by serotonergic and dopaminergic neuromodulatory systems, all hallmarks shared with more complex decision-making. Through a forward genetic screen we have identified the vertebrate-specific G-protein coupled extracellular calcium-sensing receptor (CaSR) as a key regulator of this sensorimotor decision-making. We show that acutely modulating CaSR activity bidirectionally tunes the decision-making bias of larvae, and acute Gαi/o and Gαq/11 signaling are critical for this bias. Our genetic screen also revealed that the AP2 Adaptor Protein Complex which regulates CaSR trafficking is also critical for appropriate decision-making bias. Finally, we have identified changes in the activity of key circuit components underlying these decision-making alterations through functional neural imaging of partially restrained and free-swimming larvae to elucidate how serotonergic signaling and CaSR function influence simple decision-making.

RA Jain1, MA Wolman2, KC Marsden3, C Szi1, GC Peet1, M Granato4

1Department of Biology, Haverford College, Haverford, PA, USA. 2Department of Integrative Biology, University of Madison, Wisconsin, Madison, WI, USA. 3Department of Biological Sciences, North Carolina State University, Raleigh, NC, USA. 4Department of Cell & Developmental Biology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. Funding Support: NINDS F32

15:15 *Kurt Marsden*

Genetic and neural circuit analysis of the acoustic startle threshold

ABSTRACT. All animals must make fundamental decisions about which environmental stimuli warrant a response by setting thresholds for their behavior. For example, the acoustic startle response is a highly conserved and essential survival behavior that is triggered by intense

sounds that are perceived as threatening. Proper regulation of this response requires establishing a threshold to respond appropriately to threats yet ignore innocuous sounds. The importance of maintaining an appropriate startle threshold is underscored by the fact that heightened startle sensitivity is observed in many cases of schizophrenia, anxiety, and autism. In a recent high-throughput, genome-wide screen using larval zebrafish, cytoplasmic Fragile X Mental Retardation Protein (FMRP)-interacting protein 2 (cyfip2) was identified as a key regulator of the acoustic startle threshold, with cyfip2 loss of function causing acoustic startle hypersensitivity. Here we will present new results revealing cellular and molecular mechanisms of cyfip2-dependent startle threshold regulation. Using pharmacological and targeted mutagenesis approaches, we show that cyfip2 controls the startle threshold through its actin-regulatory function. And with a simultaneous neural activity and behavior imaging technique, we show that cyfip2 acts to dampen the activity of a population of hindbrain excitatory interneurons, spiral fiber neurons, to maintain normal sensitivity. Finally, we will show validation of a second hypersensitive mutant as a mis-sense allele of the reelin receptor, vldlr. Together, this work has identified direct links between two key neurodevelopmental genes, their cellular and molecular substrates, and the control of a clinically important behavioral threshold.

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startle threshold through its actin-regulatory function. And with a simultaneous neural activity and behavior imaging technique, we show that cyfip2 acts to dampen the activity of a population of hindbrain excitatory interneurons, spiral fiber neurons, to maintain normal sensitivity. Finally, we will show validation of a second hypersensitive mutant as a mis-sense allele of the reelin receptor, vldlr. Together, this work has identified direct links between two key neurodevelopmental genes, their cellular and molecular substrates, and the control of a clinically important behavioral threshold.

JC Deslauriers1,2 and KC Marsden1,2,3

1 Department of Biological Sciences, 2 Genetics Graduate Program, 3W.M. Keck Center for Behavioral Biology, North Carolina State University, Raleigh, North Carolina, USA

15:30-16:00 Coffee Break

16:00-17:00 Session 14: Workshop

Professional Development Workshop

GBB 2019: GENES, BRAIN AND BEHAVIOR 2019

PROGRAM FOR MONDAY, MAY 13TH

Days: previous day next day all days

View: session overview talk overview

08:30-08:55 Session 15: Registration

09:00-11:00 Session 16: Symposium 4

Exposure to alcohol or other drugs of abuse during development

CHAIRS: *Stephen Boehm* and *Kristin Hamre*

09:00 *Kristin Hamre*
Symposia Introduction

09:10 *Jessica Baker*
Effect of Genetics on Neuroinflammatory Responses Following Neonatal Ethanol Exposure in BXD Mice

ABSTRACT. Fetal alcohol spectrum disorders (FASD) is the leading preventable neurodevelopmental disorder in the Western world. One hallmark of FASD is cell death in central nervous system which has been linked to neuroinflammatory responses after developmental alcohol exposure. Genetics have been shown to have a role in the severity of alcohol's effect on the developing brain as well as influence neuroinflammatory responses. In the present study, we aim to test whether there is an interaction between genetics and neuroimmune responses following neonatal ethanol exposure using C57Bl/6J (B6), DBA/2J (D2) mice and previously identified BXD recombinant inbred strains that show differential susceptibility to ethanol-induced cell death in the developing hippocampus. Neonatal mice were treated on postnatal day (P) 7 during the brain growth spurt, a time equivalent to the third trimester in humans. Animals received a subcutaneous injection of either 5.0g/kg ethanol in saline solution or isovolumetric saline given in two equal doses two hours apart. Animals were sacrificed 7 hours after initial ethanol exposure. Expression of neuroinflammatory markers were examined in the hippocampus using RT-qPCR, including Il1β, Tnf-α, Ccl2, and Il6. Variables examined were

treatment, strain, and sex, and their interactions. Different markers showed differential expression with effects of strain observed in some and strain-by-treatment effect found in others. For example, pro-inflammatory markers were differentially expressed in BXD strains with high ethanol-induced cell death but not differentially expressed in strains with low ethanol-induced cell death. These results demonstrate a complex interaction between genetics, neuroinflammatory markers, and developmental alcohol exposure.

JA Baker1, JW Johnson2, CJM Kane2, KM Hamre1

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Funding Support: NIAAA (USA) F31AA026498, R01AA018834, R01AA024695, R21AA023723, R01AA023508, P30GM110702, & UTHSC/UAMS CORNET Award

09:35 *Jennifer Thomas*

Choline as a treatment for fetal alcohol spectrum disorders

ABSTRACT. Prenatal alcohol exposure disrupts physical, neurological and behavioral development, leading to a range of fetal alcohol spectrum disorders (FASD). Nutritional factors may modify alcohol's teratogenic effects. In fact, using an animal model, we have found that supplementation with the essential nutrient, choline, can reduce the severity of a number of behavioral alterations associated with prenatal alcohol exposure, whereas choline deficiency exacerbates ethanol’s damaging effects. Choline levels during the early development, in particular, influence performance on tasks that depend on the functional integrity of the hippocampus. But how choline affects hippocampal structure and function remain unknown. In the present study we examined the effects of choline on bi-directional hippocampal plasticity. Prenatal alcohol exposure impaired long-term potentiation (LTP) in the dentate gyrus; choline supplementation enhanced LTP in both ethanol-exposed and controls subjects and may also facilitate long-term depression. These data are the first to demonstrate that choline may improve hippocampal function, complementing our previous data showing that choline likely acts via several mechanisms to alter hippocampal development. Importantly, there are also genetic

differences in choline metabolism, which could influence risk for FASD, as well as responsiveness to choline intervention. Understanding how genetic and nutritional factors modify prenatal alcohol effects has important implications both for prevention and treatment of FASD, particularly as choline supplementation is currently being investigated in clinical trials.

JD Thomas1, BR Christie2

1Center for Behavioral Teratology, San Diego State University, San Diego, CA, USA; 2Division of Medical Sciences, University of Victoria; Department of Psychology, San Diego State University. Funding Support: AA012446

10:10 *Judit Garcia-Gonzalez*

Behavioural effects of developmental exposure to the synthetic cannabinoid JWH-018 in wild type and disrupted in schizophrenia 1 (DISC1) mutant zebrafish

ABSTRACT. Cannabinoid misuse is an establish risk factor for psychiatric disorders and represents a public health issue. The increase in risk for psychiatric disorders is stronger for individuals at genetic risk or when consumption happens during brain development but the underlying mechanistic role for the association between cannabinoid consumption and psychiatric disorders remains not well understood. Recent advances in genetic manipulation and behavioural research make zebrafish (Danio rerio) a suitable model to study the short and long-lasting effects of developmental exposure to drugs.

The aims of this study are (1) to investigate whether the developing central nervous system is susceptible to the effects of the psychoactive ingredients of synthetic cannabinoids, namely JWH-018, using zebrafish as a model and (2) to test whether the effects of JWH-018 in larvae and adult zebrafish are moderated by loss of function mutations in Disrupted In Schizophrenia 1 (Disc1), a gene previously associated to psychopathology in human association studies. Zebrafish embryos exposed to JWH-018 showed increased locomotion at high doses and reduced response to startle stimuli at lower doses. During adulthood, zebrafish exposed to JWH-018 showed decreased anxiety-like behaviour.

This is the first study looking at the behavioural effects of early developmental exposure to JWH-018, suggesting that exposure to this drug during early-development leads to short-term

behavioural changes in zebrafish. Although further studies in human populations are needed to confirm the effects of synthetic cannabinoids during pregnancy, these results add further evidence to the increased risk for psychiatric disorders after exposure to cannabinoids during pregnancy.

Judit García-González1, Bruno De Quadros1, Maroua Akkari1, Caroline H. Brennan1†

1Department of Experimental and Biological Psychology. School of Biological and Chemical Sciences, Queen Mary, University of London.

10:30 *Michael Smoker*

Conditioned reward following edible ∆9-tetrahydrocannabinol (THC) consumption in adolescent and adult mice

ABSTRACT. Adolescence is a developmental period marked by numerous behavioral changes, including an increase in recreational drug use. Cannabis use is often initiated during this period, and its daily use is more prevalent than that of alcohol or tobacco among U.S. high school students. In addition, adolescents typically find cannabis's primary psychoactive component, ∆9-tetrahydrocannabinol (THC), to be less aversive than adults. Nevertheless, it has yet to be demonstrated that adolescent rodents find THC rewarding using place conditioning. Using an edible THC self-administration procedure in an inbred mouse strain (C57BL/6J (B6)) with a propensity for consuming psychoactive substances, the conditioned rewarding properties of various edible THC doses in adolescents and adults were assessed. Results will be compared to those following experimenter-administered (injected) THC. Adolescents differed from adults on a number of edible THC-related measures, including consumption, locomotor response, and place conditioning. Furthermore, preliminary evidence suggests that subsequent compulsive-like self-administration of alcohol is impacted following edible THC consumption, an effect which might be age-dependent. Taken together, these data suggest that adolescents differ from adults in their use of and response to edible THC, which could have a protracted impact on subsequent substance use. Modeling self-administration of THC during the developmental period in which most humans initiate its use will aid in understanding the particular, concurrent and protracted behavioral and neurobiological consequences resulting therefrom.

MP Smoker1,2, SL Boehm1,2 1Department of Psychology, 2Indiana Alcohol Research Center, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA: Indiana Clinical and Translational Sciences Institute, funded in part by NIH/National Center for advancing Translational Sciences (UL1 TR001108); and NIH/NIAAA (AA00761).

10:55 *Stephen Boehm*
Symposia Discussion

11:00-11:30 Coffee Break

11:30-12:30 Session 17: Selected Talks 2

Themed Talks

New or improved methodology

CHAIR: *John Crabbe*

11:30 *Patrick Martin Nolan*
Aberrant vesicular release in mice with a Vamp2 transmembrane mutation underlies striking sleep deficits

ABSTRACT. Using a non-invasive sleep surrogate as a high-throughput phenotyping tool (immobility-defined sleep using video tracking software), we screened for primary recessive sleep phenotypes in ENU G3 pedigrees. Among the pedigrees screened, we focused on one where multiple individuals expressed reduced immobility-defined sleep relative to the entire population screened. To validate these findings, EEG recordings in affected individuals revealed striking differences during NREM sleep while, surprisingly, time spent in REM sleep was dramatically reduced. Mapping and whole genome sequencing of an affected individual revealed a single mis-sense mutation in the transmembrane region of the vesicular SNARE protein, VAMP2. Investigations into the nature of the mutation were driven by observations that this allele was quite distinct from either heterozygous or homozygous Vamp2 null mutant mice. The mutant protein is less stable than wildtype, steady state levels being 25-65% of wild-type levels depending on brain region. Furthermore, discrepancies in phenotype suggested that remaining mutant protein may interfere with SNARE protein zippering, membrane pore opening and/or vesicular release. Consequently, electron microscopy and electrophysiological recordings in hippocampal slices confirmed a deficit in vesicular release in mutants. Further investigations using a fluorescence vesicular release reporter in primary hippocampal neurons indicated that the vesicular

release probability pv was profoundly decreased in homozygous neurons. The study confirms that rapid hierarchical screening tools remain a reliable approach towards high-throughput gene discovery while it highlights the relevance of synaptic mechanisms in complex behavioural processes such as sleep regulation.

Gareth Banks1, Mathilde Guillaumin2, Petrina Lau1, Erica Tagliatti3, Vladyslav Vyazovskiy2, Kirill Volynski3, Stuart Peirson2, Patrick M Nolan1

1MRC Harwell Institute, Mammalian Genetics Unit, Harwell Campus, Oxfordshire, OX11 0RD, UK. 2Sleep and Circadian Neuroscience Institute (SCNi), Nuffield Department of Clinical Neurosciences, University of Oxford, UK. 3University College London, Institute of Neurology, Queen Square, London, WC1N 3BG, UK. Funding MRC, MC_U142684173.

11:45 *David Ashbrook*

Sequencing the BXD family, a cohort for experimental systems genetics and precision medicine

ABSTRACT. The BXD mouse family is the most deeply phenotyped mammalian model system, with >7000 classical phenotypes in GeneNetwork.org. GeneNetwork allows examination of complex interactions between gene variants, phenotypes from different biological levels, and environmental factors. The family consists of 152 inbred strains, each of which is a unique mosaic of alleles from the C57Bl/6J and DBA2/J parents. We have carried out 40X sequencing of 152 BXD strains using a Chromium linked-read strategy, with mean fragment length of 44kb. We have increased the number of known, segregating, small variants in the BXD to >6 million, and are working on large structural variants. Most variants segregate with an ~50/50 allele frequency, making them ideal for mapping. We have produced a draft ‘infinite marker map’, intended to identify every recombination event in the BXD family. Analysis with this draft map shows an improvement in both mapping power and precision. We also confirmed ~15,000 epoch specific variants, mainly clustered in ~1300 regions of the genome. These variants occurred in the parental strains over the 40 years between the first and last set of BXD strains being produced. Identification of private variants allowed predictions of variants causing strains to be outliers for phenotypes in GeneNetwork. Three genes are candidates for an abnormal memory and anxiety phenotype in BXD74. This

family is an excellent resource for testing networks of causal and mechanistic relations among millions of molecular and organismal traits, including, addiction, neurodegeneration, and longevity. Full sequencing of all lines has only increased its usefulness.

David G. Ashbrook1, Danny Arends2, Pjotr Prins1, Megan K. Mulligan1, Suheeta Roy1, Evan G. Williams3, Cathleen Lutz4, Alicia Valenzuela4, Casey Bohl1, Jesse Ingels1, Melinda McCarty1, Arthur Centeno1, Johan Auwerx6, Saunak Sen7, Lu Lu1, Kelley Harris8, Abraham Palmer9, Yu-yu Ren9, Jonathan K Pritchard10, Andrew G. Clark11, Robert W. Williams1

1. Department of Genetics, Genomics and Informatics, University of Tennessee Health Science Center, Memphis, TN, USA 2. Lebenswissenschaftliche Fakultät, Albrecht Daniel Thaer-Institut, Humboldt-Universität zu Berlin, Invalidenstraße 42, Berlin, Germany 3. Department of Biology, Institute of Molecular Systems Biology, ETH Zurich, Zurich, Switzerland 4. Mouse Repository and the Rare and Orphan Disease Center, The Jackson Laboratory, Bar Harbor, ME USA 5. Division of Evolution & Genomic Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Oxford Road, Manchester, UK 6. Laboratory of Integrative and Systems Physiology, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland 7. Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA 8. Department of Genome Sciences, School of Medicine, University of Washington, Seattle, WA, USA 9. Institute for Genomic Medicine, Department of Psychiatry, University of California San Diego, La Jolla, CA, USA 10. Department of Genetics, Stanford University, Stanford, CA, USA, 11. Department of Molecular Biology & Genetics, Cornell University, Ithaca, NY.

12:00 *Gareth Banks*

Co-housing affects mouse activity rhythms in a genotype and sex specific manor

ABSTRACT. Although behavioural studies in mice are generally performed on individual animals in an isolated out-of-cage setting, their housing status prior to this is never systematically recorded. At present it is poorly understood how individual animals adapt to a group housed environment and how challenges arising from such interactions may influence downstream phenotyping. We have used the Actual Analytics HCA system (Bains et al 2016) to analyse how

co-housing two mouse strains with strikingly divergent daily activity patterns (C57BL/6J and FVB/NCrlBRH) affects the individual animals within the cage. We demonstrate a variety of strain and sex specific differences in the extent to which an individual adapts to the activity rhythms of its cage-mates. For example, while male C57BL/6J animals are largely unaffected by the presence of others in their cage, male FVB/NCrlBRH animals more readily synchronise to the activity patterns of their cage-mates. We also demonstrate that these changes are dependent upon the age at which co-housed individuals are introduced into a cage and that some changes persist when the animal is removed from the group housed environment and placed into single housing. In conclusion, this work highlights the complexity of home cage synchronicity upon individual animals. Furthermore, this data highlights that the number and genotypes of animals in a cage may have a profound effect on downstream phenotyping performed on mouse models.

Gareth Banks1, Rasneer S. Bains1, Rowland R. Sillito2, Douglas Armstrong3, Sara Wells1 and Patrick M. Nolan1.

1. MRC Harwell Institute, Harwell, Oxfordshire, UK 2. ActualAnalytics, Wilkie Building, Teviot Row, Edinburgh, Scotland 3. Institute for Adaptive and Neural Computation, University of Edinburgh, Scotland

12:15 *John Williams*

Clustering the Spectrum: Finding Genetic Associations for Autism-related Traits

ABSTRACT. Neurobehavioral conditions, such as autism spectrum disorder, are phenotypically and genotypically complex. Not only do autistic children present with deficits in multiple behavioral domains, but monogenic causes revealed by traditional GWAS cannot account for non-linear genetic interactions contributing to autism-related traits. In this work, we first mined autism diagnostic tests for behavioral processes and phenotypes, incorporating these into the Neuro Behavior Ontology. Next, we performed genome-wide association testing for SNPs and copy number variation to annotate, for the first time, 30 novel behavioral traits in children with autism from the Simons Simplex Collection. We then used machine learning (Iterative Random Forest) to detect stable epigenetic interactions among novel behavioral traits and SNPs, creating networks of genomic loci to explain partial heritability for each trait. Many traits were

associated with known autism-related loci. Amongst even highly-related behavioral traits, groups of associated loci had inverse effect sizes, highlighting the diversity of gene/phenotype associations in one autism cohort. Additionally, we created a network of autism-related phenotypic traits and associated genes to interrogate how genomic loci differentially affect behavioral traits in this population, expanding the power of the network by including links between genes co-expressed in the frontal cortex in humans. Altogether, this network approach prioritizes communities of genes associated with novel autism-related traits for patient stratification and, in the future, personalized medicine approaches.

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12:30-13:30 Lunch Break

13:30-14:30 Session 18: Distinguished Investigator Award

Distinguished Investigator Award

Dr. Seth Grant

CHAIR: *Richard Radcliffe*

13:30 *Seth Grant*

Searching for the molecular building blocks of behavior

ABSTRACT. By the end of the 19th Century, the concept that all organisms, including humans, use a behavioral repertoire of innate and learned behavior was well established. At the same time Cajal and others offered a mechanistic explanation in which each behavior was to be found in a connected set of neurons and that learning occurred by increasing the stable strength of communication between neurons. This connectionist mechanism remains as the dominant theory in neuroscience to this day. I will describe the unexpected twists and turns in a journey that started 30 years ago when molecular biology was first applied to the study of synapses and behavior. Our findings have taken us to a new theory called the Synaptomic theory which revises and extends the connectionist theory. The Synaptomic theory explains how the repertoire of

innate and learned behaviors can be stored and recalled using the remarkable complexity of the synapse proteome and the diversity of synapses in the synaptome, and how the more than 100 brain diseases disrupting postsynaptic genes cause their behavioral phenotypes.

14:30-15:30 Session 19: Business Meeting

Business Meeting

15:30-17:30 Session 20: Poster Session

Poster Session II

Even Number Posters

15:30 *Antonia Savarese*

P2 – Glucocorticoid receptor dysregulation as a genetic risk factor for high-risk ethanol intake in HDID-1 mice

ABSTRACT. Binge drinking is a major predictor of alcohol use disorder (AUD). Glucocorticoid receptor (GR) has been implicated in AUD, but GR dysregulation has not yet been identified as a genetic risk factor in non-dependent animals. Here, we examine the effects of compounds that modulate GR activity, mifepristone and tacrolimus, in a binge-like drinking task (DID) in the High Drinking in the Dark (HDID-1) mice. HDID-1 mice of both sexes were tested in a 2-day DID procedure, with drug/vehicle administered prior to 20% ethanol access on Day 2. Intake was evaluated after 2-hours of access on both days and 4-hour access on Day 2, after which blood was collected for blood ethanol concentration (BEC) analysis. In subsequent weeks, water and saccharin intake were also evaluated. Mifepristone and tacrolimus both reduced ethanol intake (g/kg) and BEC levels relative to vehicle, with no sex differences emerging. Neither drug reduced water intake, but tacrolimus reduced saccharin intake (ml/kg). In summary, HDID-1 mice exhibit a rapid behavioral response to mifepristone and tacrolimus, suggesting GR is dysregulated in these genetically at-risk mice. Our lab is currently examining gene expression of GR and its regulator proteins (FKBP51, FKBP52) in HDID-1 mice and their low-drinking founder line, HS/Npt, to determine whether selection has produced a sensitized GR system, and we are testing specific antagonists to GR (CORT113176) and FKBP51 (SAFit2) in HDID-1 mice. We are also exploring whether mifepristone reduces drinking by increasing the aversive properties of ethanol in an ethanol conditioned taste aversion task.

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Support: VA Grant 101 BX000313; by NIAAA grants AA020245, AA013519, AA007468, and AA010760; and by the family of John R. Andrews

15:30 *Catherine Doust*

P4 – The effect of dyslexia candidate genes on reading and language abilities in an adult population cohort

ABSTRACT. Reading and language abilities are critical factors for educational achievement and success in adulthood. These traits are highly heritable, but their underlying genetic architecture is largely undetermined. Genetic studies of reading and language traditionally focus on children with developmental disorders, however unselected adult samples would provide larger sample sizes thereby increasing power to identify genetic factors of small effect size. Here, we introduce an Australian adult population cohort (42 – 73 years of age, N = 1,195) with validated measures of reading and language ability, including non-word reading to assess phonological processing: a core component of reading skill. Genome-wide association was performed for a reading and spelling composite score, non-word reading, phonetic spelling, non-word repetition (a marker of language ability), and self-reported reading impairment. Here we focus only on replicating previous single nucleotide polymorphisms (SNPs) and genes associated with dyslexia and specific language impairments (SLI), for which we are sufficiently powered.

In gene-based tests, FOXP2, a well-established language gene, was identified in the top three most significant genes for non-word repetition (p = 1.21 x 10-4). The dyslexia candidates MRPL19and S100B were significantly associated with phonetic spelling (p = 3.11 x 10-2) and non-word repetition (p =4.58 x 10-2) respectively. For the reading and spelling composite score, SNPs rs9722 and rs9467075, previously associated with dyslexia, were significant (p = 1.67 x 10-2; 2.27 x 10-2 respectively) and seven further previously-reported SNPs (rs17236239, rs2710102, rs759178, rs600753, rs2538976, rs2538991 and rs807701) were significantly associated with non-word reading. Gene-set

analyses of 14 candidate dyslexia genes and five SLI genes were not significant, but the neuron migration pathway was significantly associated with the composite reading and spelling score (p = 3.68 x 10-2). This research contributes to the identification and replication of genetic factors in reading and language disorders, crucial for understanding their aetiology and informing intervention strategies.

Presented by Catherine Doust (PhD Candidate, University of Edinburgh) Authors: Scott D Gordon, Nicholas G Martin, Simon E Fisher, Timothy C Bates, Michelle Luciano

15:30 *Lilah Glazer*

P6 – Low-level embryonic exposure to methylmercury causes neurobehavioral impairment in larval and adult zebrafish

ABSTRACT. Methylmercury (MeHg), an organic form of the heavy metal mercury, is one of the most neurotoxic environmental pollutants, demonstrated to have high potency for causing developmental neurotoxicity even at low levels. Yet, the role of prenatal MeHg exposure in the aetiology of neurodevelopmental disorders is controversial. In this study, we investigated the life-long behavioural effects of developmental exposure to low-levels of MeHg, below those causing overt toxicity, using the zebrafish model. Embryos were exposed to non-dosed water or water containing 5-30 nM MeHg from 6 hours post fertilization (hpf) for 96 h, then washed and transferred to non-dosed water for the remainder of the experiment. At 6 days pf (dpf), larvae were tested for locomotor activity in response to alternating light and dark conditions. To determine the long-term effects, developmentally exposed adult zebrafish were tested in a behavioral battery including assays for anxiety-related behavior, social affiliation, and sensorimotor response and habituation. Our results indicate that developmental exposure to MeHg caused a long-term increase in anxiety-related response in both the larvae and the adult fish. In addition, there is indication for motor deficits at higher levels of exposure. These results and their possible mechanisms of action will be discussed, as well as translational importance and future directions.

Supported by Marie Curie Individual Fellowship

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15:30 *Paige Chandler*

P8 – From sleep to schizophrenia: Investigating the region-specific function of Zfhx3 in the mouse brain, and characterising its molecular activity

ABSTRACT. Zinc finger homeobox 3 (Zfhx3) is a brain-region enriched transcription factor that binds to AT motifs in promoter and enhancer regions. In humans, coding sequence mutations have been linked to a range of diseases, including schizophrenia. Through the investigation of missense and null mutations by our group, Zfhx3 has been shown to have an important role in transcriptional regulation of neuropeptides and their receptors within the suprachiasmatic nucleus (SCN), allowing for the maintenance of typical circadian rhythms. In addition to the SCN, data from the Allen Brain Atlas show Zfhx3 expression within other regions of the mouse brain, including dopaminergic regions such as the ventral tegmental area and the substantia nigra. Zfhx3 is also upregulated in the cortex of schizophrenic patients. Given the dopaminergic hypothesis of schizophrenia, the upregulation seen in the cortex, and the genetic associations, we wish to further investigate the contribution of Zfhx3 to schizophrenia-related behavioural changes in mice. We are investigating the distribution of Zfhx3 expression within dopaminergic regions and identifying specific cell types using double immunofluorescence labelling. So far we have identified that while Zfhx3 is expressed in most dopaminergic neurons, it is also expressed in other cell types. We have also established a DAT-Cre driven Zfhx3 knockout mouse – a conditional knockout mouse model which deletes Zfhx3 only in dopaminergic cells. These mice have been subjected to a behavioural phenotype pipeline, focused on schizophrenia-related endophenotypes. We discuss the biological relevance of these findings, particularly in how they relate to dopaminergic function in physiology and disease.

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15:30 *Tsuyoshi Miyakawa*

P10 – Systematic analysis of brain pH and lactate levels in animal models: relationships

and implications for behavioral outcomes

ABSTRACT. Decreased pH has been observed in the postmortem brain of patients with particular psychiatric disorders; however, it remains controversial whether this phenomenon is a primary feature of these diseases or a result of confounding factors. In our recent studies involving mouse models of schizophrenia, bipolar disorder, and autism spectrum disorders, we found that a decrease in brain pH, along with an increase in lactate levels, may be the underlying pathophysiology of these psychiatric disorders, rather than a mere artifact. Thus, we launched the Brain pH project, with the aim of improving our understanding of the prevalence of brain pH changes, particularly those that occur in psychiatric disorders, using animal models. Thus far, we have analyzed brain pH and lactate levels within 37 models of animals, including genetically modified mice, drug-treated mice, and mice that have undergone other experimental manipulations. Among the animal models examined, 12 showed changes in either or both brain pH and lactate levels. Importantly, meta-analysis of those data revealed a highly significant negative correlation between brain pH and lactate levels, suggesting that the increased lactate levels may lead to reduction of brain pH, whereas reduced lactate levels may lead to increased brain pH. We combined the biochemical data with behavioral data (e.g., data available from the Mouse Phenotype Database: http://www.mouse-phenotype.org/) to investigate the relationships of brain pH and lactate levels with behavioral outcomes, such as locomotor activity, anxiety-like behaviors, and working memory performance. We will discuss our interpretations of the relationships demonstrated in this analysis.

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Shigeo Okabe23, Herbert Y Meltzer24, Tsuyoshi Miyakawa1

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15:30 *Wim Crusio*

P12 – Ultrasonic communication in the CB1 knockout mouse line during development and at adulthood

ABSTRACT. The endocannabinoid system (ECS) is an important modulator of neuronal functions in the mammalian brain, critically regulating the expression of several behaviors. Recent lines of evidence have suggested a role of the ECS in the control of social behaviors and their dysfunction in rodents and humans, although the precise relevance of the main cannabinoid receptor (CB1) for social intraspecific communication has not been investigated yet. Our study focused on ultrasonic (US) communication in CB1-KO mice, taking into account the relevance of age and sex differences. US emission in response to maternal separation was examined in male and female CB1-KO pups and their wild type (WT) littermates at post-natal days (PND) 4, 6, 8, and 10. US communication was then reanalyzed at adulthood, together with social interaction towards an adult female conspecific. The results clearly show a selective role of CB1 in modulating US communication, with an effect that was evident both at development and adulthood in both sexes. These data have therefore strong implications for social and communication pathologies, such as Autism Spectrum Disorders, suggesting a potential key-role of the ECS in these developmental diseases.

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15:30 *Thalia Garvock-de Montbrun*

P14 – Behavioural characterization of the MDGA2+/- mouse model of Autism spectrum disorder across the lifespan

ABSTRACT. Autism spectrum disorder (ASD) is a developmental disorder characterized by numerous behavioural symptoms, including repetitive behaviours, inhibited communication, and reduced sociability. The MAM domain-containing glycosylphosphatidylinositol anchor 2 (MDGA2) gene has been linked to ASD in humans and haploinsufficency of MDGA2 in a novel mouse model (MDGA2+/-) resulted in behavioural phenotypes seen in humans with ASD (Connor et al., 2016, Neuron. 91:1052-68). To examine the effects MDGA2 on behaviour throughout the lifespan, we tested MDGA2+/- mice (F 10, M 7) and wildtype littermate controls (F 8, M 11) on a neurodevelopmental test battery (P1 – P24). Neurodevelopmental behaviours were assessed through milestone emergence, sensorimotor, and cognitive tests. Subsequently, a behavioural battery was performed at 2, 9, and 15 months of age to examine behaviours linked to ASD. Social impairment was determined with the social affiliation test, the three-chamber test of social interaction, and social transmission of food preference. The marble burying test was used to examine motor stereotypy, while the rotarod test assessed gross motor coordination and learning. Visuospatial learning and memory was assessed with the Morris Water Maze. Results indicate some genotype, sex and age differences, which will be described in detail. We will be examining if the differences found during the neurodevelopmental stage persist throughout the lifespan. Because ASD is a behaviorally-defined disorder, it is essential to use behavioral bioassays that are sensitive to associated symptoms in any prospective mouse model of ASD. These results will help determine the value of the MDGA2+/- mouse as a translational model of ASD.

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15:30 *Ada Boutelier*

P16 – ICM-APATHY-TASKS: Developing a New Behavioral Tool to Explore the Three Underlying Mechanisms of Apathy

ABSTRACT. Apathy is defined as a quantitative reduction of goal-directed behavior (GDB). Although multidimensional model of apathy has been established, its underlying mechanisms and neural basis are poorly known. We hypothesize that at least one of the three key systems that are necessary to produce and control GDB is disrupted in apathy: motivation to act, executive abilities, and auto-activation. Each of these systems relies on a specific neuroanatomic circuitry, involving prefrontal cortex. Building on these observations we propose a new original computerized behavioral tool for exploring apathy along its three subcomponents. ICM-APATHY-TASKS (ICMAT), coding in Python, tests in interaction executive abilities (easy and difficult subtasks) and motivation (each subtask performed twice with high or low gain). Modified ICMAT includes testing of auto-activation by pursuing the task in a strongly hetero-guided, and an unguided condition. Twenty subjects in the study ECOCAPTURE 2 (Clinicaltrials.gov: NCT03272230, ends in 2020) completed the ICMAT, 10 apathetic patients with behavioral variant frontotemporal dementia (bvFTD) and 10 matched healthy controls. Twelve additional subjects completed the modified ICMAT: 7 healthy controls and 5 patients with prefrontal cortex lesion. Preliminary results in healthy subjects show a significant effect of difficulty but no effect of reward on performance. Similar results are observed in bvFTD patients. Healthy subjects perform significantly poorer in auto-initiation condition but tend to produce more activity as compared to hetero-guided condition. These results suggest that healthy subject tend to show an exploratory behavior in auto-initiation condition, i.e. activity less efficient but quantitatively higher than in hetero-guided condition. 1 FrontLAB, Inserm U 1127, CNRS UMR 7225, UPMC Paris 06 University, UMR S1127, Sorbonne University, Brain and Spinal Cord Institute (ICM), Hôpital Pitié-Salpêtrière, Paris, France.

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15:30 *Irina Fedotova*

P18 – The generalized and myoclonic seizures in Krushinsky-Molodkina rat strain

ABSTRACT. Krushinsky-Molodkina (KM) rat strain was the first one in the range of similar genetic models, created in the late 1940s. When exposed to loud sound develop clonic (in 2-3 sec) and tonic (in 7-10 sec) convulsions. The daily sound exposure results in 15-12 days) with the development of myoclonic seizures, starting with face muscle jerks spreading to neck and body musculature. This phenomenon was described in other audiogenic prone rat strains and represents the typical seizure kindling. As the TLE symptoms in humans include also numerous rather serious psychiatric disorders (apart from myoclonus fits) the KM rat strain could represent the model of complicated changes development in brain structures similar and parallel to those in humans (when the long history of generalized seizures invokes the TLE symptoms). The behavioral peculiarities defects in KM rats could be noted in locomotion, anxiety signs and tendency to develop the catalepsy – both spontaneous and post-ictal. The short seizure development latencies and the possibility to reproduce seizures in the same animals made these animals the valuable tool for study the seizure modulation factors – e.g. strong olfactory stimulation and antiepileptic drugs. The developmental aspects of audiogenic epilepsy is also promising when this strain is used as the genetic model of seizure propensity.

IB Fedotova, II Poletaeva

Biology Department, Lomonossov Moscow State University Funding Support: RFBI, grant № 18-015-00173 and the State program «Neurobiological basis of animal behavior” № NIOKTR AAAA-A16-116021660055-1»

15:30 *Helen Kamens*

P20 – ADOLESCENT SOCIAL STRESS INFLUENCES MORPHINE SENSITIZATION AND GENE EXPRESSION

ABSTRACT. Opioid misuse is a critical public health crisis in the United States. Epidemiological research has demonstrated that exposure to

stress during adolescence leads to increased substance use. Further, the most frequently reported stressors are social. Through modeling exposure to adolescent social stress in animals we can gain a greater understanding of the long-term behavioral and physiological consequences. Here we set out to determine if exposure to social stress in adolescence alters morphine responses in adulthood in C57BL/6J mice. To determine biological mechanisms that could underlie observed behavioral changes, we examined changes in gene expression as a result of adolescent stress. Male and female C57BL/6J mice exposed to adolescent social stress displayed attenuated morphine sensitization compared to control animals. In contrast, there were no differences in baseline locomotor activity between the groups or in response to an acute injection of morphine. We observed differential expression of 65 genes in the nucleus accubmens following adolescent social stress. Pathway analysis suggest long-term alterations in stress hormone signaling (corticotropin releasing hormone signaling), growth factors (VEGF signaling), and intracellular signaling pathways (CREB signaling, ERK/MAPK signaling). These results suggest that exposure to adolescent social stress changes the response to chronic opioid administration. One mechanism by which social stress may influence this behavior is by altering the normal development of the nucleus accumbens. These data provide important insight into one environmental exposure that may heighten opioid misuse.

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15:30 *Cheryl Reed*

P22 – Does tolerance to ethanol-induced sedation explain the sensitized response to ethanol?

ABSTRACT. Under conditions of repeated intermittent exposure to ethanol, a sensitized locomotor stimulant response often develops in mice. The sensitized response may be what remains after tolerance has developed to sedative effects of ethanol. Conversely, sensitization and tolerance may be unrelated. An initial study in C57BL/6J x DBA/2J recombinant inbred strains concluded that the two phenomena are not genetically related, and thus, perhaps mechanistically distinct. Here, we sampled a

more genetically diverse panel of 15 standard inbred mouse strains. Changes in activity counts and foot slip errors (a measure of ataxia in a grid balance test) across ethanol treatments indexed sensitization and tolerance, respectively. Results were strain-dependent for change in activity ($F[14,132]=8.4$, $p<0.001$) and in number of foot slip errors ($F[14,132]=1.8$, $p<0.05$). However, more active mice have greater opportunity to commit foot slips, and these traits were positively correlated ($r=0.57$, $p<0.05$). Therefore, we also examined the ratio of errors/activity counts. There was no significant effect of strain for change in this ataxia ratio, but ataxia did decrease across ethanol treatment days, indicating tolerance development. Significant differences among strains in the amount of sensitization developed in the absence of significant strain differences in tolerance development in ataxia ratio indicates that these two consequences of repeated ethanol exposure are not genetically or mechanistically related. A similar conclusion was reached when individual values for each of these traits were obtained in a heterogeneous mouse stock and level of sensitization and tolerance to ethanol were not found to correspond with each other.

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15:30 *Inga Poletaeva*

P24 – Relative brain weight differences as the result of direct and indirect selection

ABSTRACT. The differences in the brain weight - the trait, connected to the level of animal cognition,- is usually evaluated comparing the respective scores in different taxa. The selection of laboratory mice for large and small relative brain weight is one of the techniques which permit to evaluate the role of this variable at the intraspecies level. Three selection experiments were performed in our laboratory, their results being more or less similar- with higher cognitive capacities in Large Brain line and higher indices of anxiety and stress reactivity in Small Brain mice. The selection for contrast values of this trait had been stopped at the level of F22 in the third experiment, and the two lines were randomly bred, now for 15 generations. The relative brain weight and behavioral differences stayed during breeding without selection. Large Brain mice

were higher in cognitive task solution than Small Brain animals. The “puzzle-box” cognitive task was used, which requires the understanding of “object permanence rule”. At the same time the selection for high scores of cognitive task solution resulted in higher scores of the brain weight in the selected strain. This means, that in laboratory mice (very popular among neurobiologists) the brain weight values could indicate the cognitive capacities level.

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1Biology Department, Lomonossov Moscow State University. Funding: RFBI, N 16-04-01169, the State program «Neurobiological basis of animal behavior” № NIOKTR AAAA-A16-116021660055-1»

15:30 *Anna Delprato*

P26 – Sex Differences in Gene Expression Patterns Associated with the APOE4 Allele

ABSTRACT. The APOE gene encodes apolipoprotein ε (ApoE), a protein that associates with lipids to form lipoproteins that package and traffic cholesterol and lipids through the bloodstream. There are at least three different alleles of the APOE gene: APOE2, APOE3, and APOE4. The APOE4 allele increases an individual's risk for developing late-onset Alzheimer Disease (AD) in a dose-dependent manner. Sex differences have been reported for AD susceptibility, age of onset, and cognitive-related symptom progression, with females being more affected than males. In this study, we use a systems biology approach to examine gene expression patterns in the brains of aged female and male individuals who are positive for the APOE4 allele in order to identify possible sex-related differences that may be relevant to AD. Based on correlation analysis, we identified a large number of genes with an expression pattern similar to that of APOE in APOE4-positive individuals. The number of these genes was much higher in APOE4-positive females than in APOE4 positive males, who in turn had more of such genes than APOE4-negative control groups. Profiling of these genes using Gene Ontology (GO) term classification, pathway enrichment, and differential expression analysis supports the idea of a transcriptional role of APOE with respect to sex differences and AD.

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*Equal contributions

15:30 *Marina Shustikova*

P28 – Heritability of aggression in human: what may be missed and included?

ABSTRACT. This study is examined a gender-specificity of genetic and environmental factors associated with family constellation in the formation of individual differences in aggression.

Materials and methods The data were collected among 367 representatives in complete biological families with two same-sex sibs, inhabitants of Kharkiv. The aggression level was defined by BDHI. The similarity among relatives was studied by interclass / intraclass correlation coefficients. The heritability indexes was determined by Falconer`s formula.

Results In male siblings physical aggression H^2= 84%, h^2 = 24%, Gd = 60% (rsb = 0.314, p = 0.045; rpo = 0.343, p = 0.035). The variability of the level of indirect, verbal aggression and irritability depends on birth order: an increase of similarity between fathers and younger sons compared to fathers and older sons was noted. Indirect aggression: r = 0.312, p=0.069 / r = – 0.170, p=0.271. Verbal aggression: r = 0.427, p=0.011 / r = – 0.143, p=0.355. Irritability: r = 0.327, p=0.055 / r = – 0.126, p=0.415. In female siblings physical aggression h^2 = 35%, indirect aggression h^2 = 41%, irritability h^2 = 36%. The impact of birth order is not revealed.

Conclusion The heritability of physical aggression in male may included the shared environment context defined by sibling interpersonal interactions and missed the role of major or candidate genes because of high level of the effects of dominance and epistasis.

Marina Shustikova Institute of Biology, V.N. Karazin Kharkiv National University, Ukraine.

15:30 *Briana Chen*

P30 - Ovarian hormones causally contribute to the prophylactic efficacy of (R,S)-ketamine and (2R,6R)-hydroxynorketamine in female mice.

ABSTRACT. While exposure to stress is a major risk factor for mood disorders, stress does not universally cause illness. For example, although women are less likely to experience trauma than men, they are twice as likely to develop depression. We previously reported that a single injection of (R,S)-ketamine before stress protects against depressive-like behavior and attenuates learned fear in male mice. However, the prophylactic efficacy of ketamine and ketamine metabolites in female mice remain largely unknown. To address this question, female mice were administered (R,S)-ketamine, (2R,6R)-HNK, or (2S,6S)-HNK at various doses 1 week before one of a number of stressors. Prophylactic efficacy was validated using the forced swim test (FST). In a separate set of experiments, we examined whether sex hormones influenced the efficacy of prophylactic compounds. We found that (R,S)-ketamine and (2R,6R)-HNK, but not (2S,6S)-HNK, significantly reduced immobility in the FST compared to saline controls. Interestingly, in females, ketamine was prophylactic at a lower dose than previously shown in males. (2R,6R)-HNK was prophylactic at a significantly smaller dose and at a faster rate than its precursor (R,S)-ketamine. Moreover, the prophylactic efficacy of these compounds was mediated by ovarian hormones. Overall, these data indicate that (R,S)- ketamine and (2R,6R)-HNK are effective prophylactics against stress in females and that their sex-specific effects may be modulated by gonadal hormones. Our findings offer insights into the prevention of stress- related impairments in a susceptible population and may further elucidate underlying sex-specific neuropathology contributing to the onset of depression.

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15:30 *L Molina-Garcia*

P32 - Neuropeptide modulation of aversion and reward during learning

ABSTRACT. When an animal repeatedly encounters a signal coupled with either a punishment or a reward, it eventually learns to expect both to occur together in a process called associative learning. A central goal in neuroscience is to understand how neural circuits integrate conflicting (rewarding and aversive) experiences that need to be behaviourally resolved during learning.

To shed light into this process at the molecular and cellular level, we are dissecting a neural circuit for sexual conditioning in the C. elegans male.

Sexual conditioning is a form of male-specific associative learning by which a rewarding experience with mates overrides an aversive association with starvation, thus switching the males' behaviour to a stimulus from repulsion to attraction (Sakai et al., 2013). Previously, our lab implicated the Mystery Cells of the male (MCMs) interneurons and the neuropeptide PDF-1 as regulators of the sexually conditioned switch (Sammut et al., 2015).

Here we show a dual role for the neuropeptide PDF-1 in the regulation of both aversive and appetitive learning in C. elegans. By using a Cre-Lox intersectional strategy we find that PDF acts in distinct subsets of neurons to promote reward and to promote aversion. Also the molecular mechanisms underlying aversion and reward seem to be distinct: whereas only PDF-1 is required to signal reward, both PDF-1 and PDF-2 act redundantly to promote aversion. A similar dual role in encoding value has been recently described for dopamine in both mice and flies, suggesting a conserved value-assignment logic in neural circuits across evolution.

Laura Molina-Garcia1, Susana Colinas-Fischer1, Sergio Benavides-Laconcha1, Lucy Lin1 & Arantza Barrios1

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GBB 2019: GENES, BRAIN AND BEHAVIOR 2019

PROGRAM FOR TUESDAY, MAY 14TH

08:30-08:55 Session 21: Registration

Registration

09:00-11:00 Session 22: Symposium 5

Not just insulation: Oligodendrocyte function and myelination in behavior

CHAIR: *Iiris Hovatta*

09:00 *David Lyons*

Myelinated axon plasticity and neural circuit function

ABSTRACT. It has been known for over a century that myelin accelerates impulse propagation along axons. However, in recent years it has become clear that myelination in the central nervous system continues throughout life, and that it can be controlled by physiological brain function. Because regulation of the number, distribution, length and thickness of myelin sheaths along axons will all affect conduction timing and thus circuit function, it has been proposed that activity-regulated myelination might represent a fundamental form of nervous system plasticity. Recently we have demonstrated that neuronal activity regulates myelination along specific axons in the larval zebrafish CNS. We are currently investigating the mechanisms by which neuronal activity regulates myelination in vivo, using the power of zebrafish for gene targetting, optogenetics, functional imaging, and in vivo analysis of cell biology. We are also exploiting the suitability of zebrafish for longitudinal live imaging across scales, from molecule to system, to investigate how regulation of myelination affects the function of neural circuits. In one set of approaches we combine live imaging of neurons, myelinated axons, and neural circuits with electrophysiology to investigate how regulation of myelination affects axonal conduction and synaptic communication. In parallel we are asking how CNS myelination regulates population-level activity behaviour

using zebrafish imaging based approaches. With this, we hope that zebrafish will help illuminate a poorly understood aspect of neural circuit function.

David Lyons1

1. Centre for Discovery Brain Sciences, University of Edinburgh, Edinburgh EH16 4SB, United Kingdom

09:25 *Arnaud Tanti*

Long-lasting molecular and cellular effects of child abuse and depression on oligodendrocyte function

ABSTRACT. Early-life adversity (ELA), in particular child abuse, has devastating consequences on psychological development. It is amongst the strongest predictors of psychopathologies, in particular depression, and suicide. While imaging studies suggest that ELA may lead to altered trajectories of brain structural and functional development, the cellular and molecular basis of these changes are unclear. As a protracted form of brain plasticity essential to the functional maturation of the central nervous system, myelination has recently emerged as an interesting candidate to support these changes. Using a combination of molecular and histological approaches in well-characterized post-mortem samples from depressed suicides, our research aims at describing the long-lasting impact of ELA on oligodendrocyte function and myelination. Our main findings suggest that in prefrontal regions of the brain, child abuse lastingly disrupts the epigenetic and transcriptional program of myelination, modifies the balance of oligodendrocyte-lineage cells, and associates with changes in myelin properties of individual fibers. Considering the essential role of myelination in normal brain development, these changes during critical periods may possibly mediate some of the negative mental health outcomes associated with child abuse, in particular increased vulnerability to psychopathology. Beyond myelination, our recent work focuses on glial-glial interactions and oligodendrocyte contribution to extracellular matrix plasticity, one of the multiple aspects of oligodendrocyte functions which may contribute to ELA-associated prefrontal circuits remodeling.

A. Tanti1, Gustavo Turecki1,2, Naguib Mechawar1,2 1McGill Group for Suicide Studies, Douglas Mental Health University Institute, Montreal, QC, Canada. 2McGill University, Dept of Psychiatry, Montreal, QC, Canada. Support:

Fonds de Recherche du Québec – Santé; American Foundation for Suicide Prevention; ERA-NET NEURON; Canadian Institutes of Health Research.

09:50 *Mikaela Laine*

Genetic control of myelin plasticity after chronic psychosocial stress

ABSTRACT. Environmental and genetic factors interact in the development of anxiety disorders, but the underlying mechanisms remain poorly understood. Additionally, many individuals are resilient to chronic stress-associated psychiatric symptoms. To study the gene-environment interaction in psychosocial stress we used the chronic social defeat stress (CSDS) mouse model in four inbred strains [DBA/2NCrl (D2), 129S2/SvPasCrl, BALB/cAnNCrl, and C57BL/6NCrl (B6)]. To classify mice as stress-susceptible or -resilient we assessed their social avoidance behavior. We found that the behavioral response to stress was strongly moderated by the genetic background. Of the four strains, B6 was the most stress-resilient, while D2 mice were the most stress-susceptible. To examine the transcriptomic response to CSDS, we conducted RNA-seq of these two strains and found significant enrichment of myelin-related genes among the genes differentially expressed between susceptible or resilient mice compared to controls. We also measured myelin thickness by electron microscopy. We detected lower expression levels of myelin-related genes and thinner myelin in the ventral hippocampus of stress-susceptible B6, but not D2, mice. B6 susceptible mice had higher myelin-related gene expression levels and thicker myelin in the bed nucleus of the stria terminalis. In the medial prefrontal cortex, B6 resilient mice had thicker myelin on small axons, while D2 resilient mice had thinner myelin, than controls. Our results suggest myelin plasticity as one of the major brain responses to chronic psychosocial stress. Furthermore, we found brain region dependent variations in this response, and that the behavioral and transcriptomic responses to stress are genetically controlled.

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University of Helsinki, Finland, 3SleepWell Research Program, Faculty of Medicine, University of Helsinki, Finland, 4Institute of Biotechnology, University of Helsinki, Finland, 5Finnish Institute of Molecular Medicine, University of Helsinki, Finland. Funding support: European Research Council, ERA-NET NEURON, Sigrid Jusélius Foundation, and the University of Helsinki

10:15 *Hannelore Ehrenreich*

Catatonia – starting to understand mechanisms involving myelin and neuroinflammation

ABSTRACT. The etiology of catatonia, an executive 'psychomotor' syndrome seen across neuropsychiatric diseases and other medical conditions, has been obscure and its treatment unspecific. To investigate mechanisms involved in the still highly mysterious but frequent phenotype catatonia, we studied myelin mutant mice as experimental models as well as healthy and ill humans. Moreover, we approached specific preventive as well as therapeutic strategies by targeting neuroinflammation via microglia depletion. In a deeply phenotyped schizophrenia sample (N=1095), we uncovered an unexpectedly high prevalence of >25% individuals with catatonic signs. CNP rs2070106-AA, a loss-of-function genotype of a myelin-specific gene, was found associated with catatonia in two independent schizophrenia cohorts, and with white matter hyperintensities in a general population sample. Subtle defects of myelination in mouse mutants not only of Cnp1, but also of Plp1 or Mbp lead to catatonia, coinciding with microgliosis. We therefore hypothesized that neuroinflammation of myelinated tracts might be causative of catatonia and alleviated by depleting microglia. We demonstrate by behavioral phenotyping, MR-spectroscopy, and immunohistochemistry that the inhibitor of CSF1 receptor kinase signaling, PLX5622, can attenuate neuroinflammation and catatonia in Cnp1 mutants. We suggest that catatonic signs and possibly other executive function defects in white matter disease can be efficiently targeted by microglia-directed therapies.

Hannelore Ehrenreich, MD, DVM Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen, Germany

10:40 *Rachel Rahn*

The developmental trajectory of functional connectivity and sensorimotor behavior in

mice

ABSTRACT. Functional connectivity (FC) networks in human infants have been previously shown to vary in their development, with sensorimotor areas showing more connectivity than association cortex in infancy. However, the developmental trajectory of FC changes between infancy and adulthood and these changes' potential correspondence to behavioral development are not well-characterized. The objective of this study was therefore to evaluate cortical FC and sensorimotor function in the Thy1-GCaMP6f genetically-encoded calcium indicator (GECI) mouse, using longitudinal mesoscopic calcium imaging and sensorimotor behavioral assays. We hypothesized that performance on Locomotor Activity/exploration and Catwalk assays would improve as development proceeds, in parallel with an increase in homotopic motor cortex FC. Calcium and hemoglobin resting-state data were collected from Thy1-GCaMP6 mice at five developmental timepoints (postnatal day 15 (P15), P22, P28, P35, and P60). Seed-based FC displayed characteristically high correlation for homotopic contralateral regions and passed quality control metrics at all timepoints. We also evaluated the performance of P22 and P60 Thy1-GCaMP6 mice and wildtype littermates in a Locomotor Activity/exploration assay. Our preliminary analyses detected no abnormalities in distance traveled or time in center by the Thy1-GCaMP6 mouse at either developmental timepoint, suggesting typical activity and anxiety-related levels in these mice. We are currently analyzing gait-related metrics such as stride length, duty cycle, and base of support measured on the Catwalk system. Taken together, these neuroimaging and behavioral results will help elucidate the developmental trajectory of FC and sensorimotor function and can provide a reference dataset in our future studies of genetic models of neurodevelopment.

RM Rahn1,2, SM Maloney3, LM Brier2, AR Bice2, JP Culver2,4,5, JD Dougherty1,3
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11:00-11:30 Coffee Break

11:30-12:30 Session 23: Selected Talks 3

Themed Talks

Drugs of abuse and addiction

CHAIR: *Angela Ozburn*

11:30 *Winona Booher*

Alcohol Related Behaviors in Mice Selectively Bred for High and Low Activity

ABSTRACT. Winona Booher1, 2, Eliza Elliotte3, Anuradha Prakash4, Marissa Ehringer1, 2

Open-field activity (OFA) is widely viewed as proxy for measuring anxiety behavior in mice. DeFries et al. (1978) bidirectionally selected for OFA that resulted in a 7.8-20 fold difference. Mice with high OFA (high) are considered a model of low anxiety, and mice with low OFA (low) represent a model of high anxiety. The high and low strains of mice also show correlated differences in other anxiety-related behaviors including light-dark box, elevated plus maze, mirror chamber test, and elevated square maze (Henderson et al., 2004). Due to the high correlation of anxiety and alcohol use disorders (AUDs), we have begun to characterize these strains for several alcohol phenotypes. Using a two-bottle choice paradigm, it was revealed that female high mice consume significantly more alcohol than the female low mice. To evaluate acute sensitivity to alcohol, we tested these strains for the loss of righting reflex (LORR). Both male and female high mice regain their righting reflex significantly faster than the male and female low mice, respectively. This increased sensitivity to alcohol's sedative effects observed in the low mice may explain why the low mice consume less alcohol than the high mice in the two-bottle choice paradigm. In addition, we are currently testing these strains for acute alcohol induced locomotor sensitization and alcohol metabolism. Finally, because the hippocampus may play a role in both anxiety and AUDs, we have collected alcohol naïve brains for hippocampal RNA sequencing to examine differential gene expression between both male and female high and low mice.

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11:45 *Amanda Barkley-Levenson*

Glyoxalase 1 involvement in ethanol reward sensitivity and ethanol withdrawal

ABSTRACT. The gene glyoxalase 1 (Glo1) has been previously implicated in anxiety- and depression-like behaviors in mice, and also in binge-like ethanol consumption. Transgenic mice overexpressing Glo1 show increased ethanol consumption and anxiety- and depression-like behaviors. In contrast, genetic knockdown of Glo1 or pharmacological inhibition of the enzyme leads to lower levels of drinking and lower anxiety- and depression-like behaviors. To further characterize the role of Glo1 in ethanol-related behaviors, we investigated whether genetic or pharmacological manipulations could alter ethanol reward sensitivity and ethanol withdrawal severity. Transgenic mice overexpressing Glo1 and wild type littermates were tested for ethanol conditioned place preference (CPP). Transgenic mice acquired significant CPP after four conditioning trials, whereas wild type mice required eight trials. In a separate experiment with wild type mice, treatment with a GLO1 inhibitor was found to reduce ethanol CPP expression compared to vehicle. Wild type mice treated with a GLO1 inhibitor during ethanol withdrawal showed reduced seizure severity compared to vehicle-treated mice, although seizure severity was still elevated compared to control (non-withdrawal) mice. Vehicle-treated mice had significantly more anxiety-like behavior in an open field test than control mice, and inhibitor treatment completely blocked this effect. These data extend previous work with Glo1 and demonstrate its involvement in ethanol reward and both the physiological and affective effects of ethanol withdrawal. Taken together, these experiments provide further evidence that Glo1 is an important target for ethanol research and may be a potential target for novel pharmacotherapy development.

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12:00 *Jacob Beierle*

Genetic differences between BALB/cJ and BALB/cByJ substrains in opioid state-dependent reward learning, spontaneous withdrawal, and weight loss in response to oxycodone: Planting the seeds for a reduced complexity cross

ABSTRACT. Opioid dependence is a heritable substance use disorder that has reached epidemic proportions within the US, however its genetic etiology is poorly understood. Murine forward genetics can identify novel genetic factors and biological pathways relevant to the human condition, and could lead to improved therapeutics. To facilitate gene mapping of opioid addiction traits in Reduced Complexity Crosses (RCCs), we phenotyped two closely related inbred mouse substrains, BALB/cJ and BALB/cByJ, for behavioral responses to the mu opioid receptor agonist oxycodone (OXY). BALB/cJ and BALB/cByJ mice were segregated from a colony of BALB/c mice at generation F36 in 1935 and are nearly 100% isogenic. Low genetic diversity combined with high phenotypic diversity facilitates gene mapping. To capture behaviors associated with various stages of the opioid addiction process, we used our multistage addiction assessment protocol (MSAAP) to examine OXY-induced locomotion, drug-free and state-dependent conditioned place preference (CPP), acute antinociception EC50s and EC50 shifts (tolerance), spontaneous emotional/affective withdrawal, body weight loss, and protracted withdrawal. We found differences in state dependent CPP, OXY induced analgesia, acute emotional/affective withdrawal, and body weight loss in response to OXY. Together, the increased state dependent OXY-CPP and spontaneous OXY withdrawal paired with increased antinociceptive potency and increased OXY-induced weight loss suggest BALB/cJ mice are generally more sensitive to the behavioral and physiological effects of OXY than BALB/cByJ mice. Future studies will employ a systems genetic approach combining behavioral QTL, expression QTL, and single cell RNA-sequencing to identify the genetic basis and molecular mechanisms underlying genetic differences in OXY phenotypes.

Jacob A. Beierle 1,2,3, Emily Yao1, Julia Scotellaro 1, Camron D. Bryant 1

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12:15 *Lisa Goldberg*

Systems genetic analysis of nicotine withdrawal deficits in learning

ABSTRACT. Cognitive deficits are a major symptom of nicotine withdrawal. These deficits are heritable, yet the genetic basis is unknown. Our lab has developed a mouse model of nicotine withdrawal deficits in learning, using chronic nicotine exposure and fear conditioning. Here, we aimed to utilize a systems genetics approach to characterize inbred strain differences and identify genetic variants underlying nicotine withdrawal deficits in learning. Thus far, male mice (n=4-13 per strain per treatment) from 21 inbred strains (C57BL/6J, BALB/cJ, CBA/J, FVB/NJ, NOD/ShiLtJ, A/J, C3H/HeJ, DBA/2J, AKR/J, DBA/1J, 129S1/SvImJ, SJL/J, SWR/J, LP/J, BTBR T+ Itpr3tf/J, NZB/BINJ, SM/J, MA/MyJ, 129S4/SvJaeJ, 129S8/SvEvNimrJ,129-Elite) received either chronic saline or nicotine (12.6 or 18 mg/kg per day for 12 days), and then were tested for hippocampus-dependent learning deficits using contextual fear conditioning. We have replicated a previously observed deficit in the C57BL/6J and identified SJL/J as exhibiting enhanced learning during withdrawal from chronic nicotine. Additionally, we are utilizing the BXD panel to identify genetic variants underlying these differences. Male and female mice (n=6-11 per sex per strain, 31 strains) were tested for contextual fear conditioning after receiving either chronic saline or nicotine (6.3 mg/kg per day for 12 days). Quantitative trait locus (QTL) mapping analyses using GeneNetwork identified a significant QTL on chromosome 4 (82.4 Mb, LRS =23.74, p<0.05). Utilizing publicly available hippocampal gene expression data from naive animals, we identified 4 positional candidates (Ptprd, Tyrp1, 2310067E19Rik, Nfib). To expand upon these positional candidates and identify hippocampal transcriptome changes associated with nicotine withdrawal, we will soon complete mRNA-sequencing in the BXD lines exhibiting extreme phenotypic variation.

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2Department of Anesthesiology, Perioperative, and Pain Medicine, Stanford University School of Medicine

12:30-13:30 Lunch Break

13:30-15:30 Session 24: Symposium 6

Molecules and connected cells

CHAIR: *Daniel Goldowitz*

13:30 *Seth Grant*

Genetic dissection of postsynaptic function in behaviour and physiology

ABSTRACT. Although mice carrying engineered mutations have provided a wealth of insights into the molecular and physiological mechanisms of behaviour, each of these studies have typically reported a single mutant and because different laboratories use non-standardized protocols there is an absence of quantitative data enabling comparison of phenotypes and metaanalyses. We have studied 58 lines of mice using a standardized pipeline in a single facility and generated a resource including behavioural measures in five apparatus that generated innate and learned responses; hippocampus slice electrophysiology using multielectrode arrays; and hippocampus transcriptome data. The targeted genes encode different classes of proteins in the postsynaptic proteome of excitatory synapses. These data reveal unexpected findings leading to a novel model for the synaptic basis of innate and learned behaviour.

14:00 *Dan Goldowitz*

Time-course transcriptome created by next-generation sequencing to find coding and non-coding genes involved in cerebellar development and function

ABSTRACT. The beginnings for providing a deep understanding of the brain in development and disease is at the genome. Moving outward there are networks of genes that are expressed at specific times and in specific cells that orchestrate neurodevelopment. The focus of this presentation is on the richness of the FANTOM5 transcriptome dataset to identify both coding and non-coding elements in mouse cerebellar development, as a proxy for the larger brain and in the context studies to identify genes involved in neurodevelopmental disorders. Novel long non-coding RNAs and enhancers RNAs are identified that could regulate gene expression. And genes novel to cerebellar development have been identified through bioinformatic mining of these data. We look forward to moving this data to the human to help identify the gene-based etiology of neurodevelopmental disabilities.

Dan Goldowitz Centre for Molecular Medicine and Therapeutics, Dept of Medical Genetics, Univ British Columbia

14:30 *Catharine Rankin*

Systematic phenomics analysis of ASD-associated genes defines novel shared and unique functions and identifies parallel genetic networks underlying hypersensitivity and impaired habituation

ABSTRACT. A major challenge facing Autism Spectrum Disorder (ASD) is the large and growing number of genes and gene variants of unknown functional significance. Here, we used Caenorhabditis elegans to systematically functionally characterize ASD-associated genes in vivo. Using our custom machine vision system we quantified 26 phenotypes spanning morphology, locomotion, sensitivity, and habituation learning in 87 strains each carrying a mutation in an ortholog of an ASD-associated gene. We identified hundreds of novel genotype-phenotype relationships ranging from severe developmental delays and uncoordinated movement to subtle deficits in sensory and learning behaviours. We clustered genes by similarity in phenomic profiles and used epistasis analysis to uncover parallel and convergent networks centered on CHD8●chd-7 and NLGN3●nlg-1 that underlie hypersensitivity and impaired habituation. We then leveraged our data for in vivo functional assays to gauge missense variant effect. Expression of human NLGN3 in nlg-1 mutant C. elegans rescued their hypersensitivity and habituation impairments, confirming functional conservation. We then tested the rescuing ability of all ASD-associated neuroligin variants, revealing varied partial loss-of-function despite proper localization. Finally, we used CRISPR-Cas9 Auxin Inducible Degradation to determine if phenotypic abnormalities caused by developmental loss of nlg-1 can be reversed by adult expression. This work charts the phenotypic landscape of ASD-associated genes, offers novel in vivo variant functional assays, and therapeutic targets for ASD

Troy McDiarmid1, Manuel Belmadani2, Joseph Liang1, Fabian Meili1, Kota Mizumoto3, Kurt Haas1, Paul Pavlidis1,2, Catharine Rankin1

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15:00 *Douglas Armstrong*

Network topology analysis of the synaptic proteome reveals molecular substructures associated with neurodevelopment, autism and intellectual ability

ABSTRACT. The synaptic proteome is widely believed to be the molecular machine that underpins the core functions of neurons – the integration and transfer of information from one cell to another. Perhaps unsurprisingly it is enriched for proteins whose genes are linked to a wide range of human neurological conditions. However GWAS datasets from these conditions map less clearly onto the synaptic proteome often with weak or no significant enrichment. The synaptic proteome can be subdivided, on the basis of network topology into clusters that each have enriched functional associations. We hypothesised that these topological communities form natural groups for gene set analysis and contain information not only about protein encoding genes with a mechanistic association with the phenotype but also with interaction partners whose role is important but less direct. We combined 30 published synaptic proteomic studies from 2000 to date to obtain a list of 6500 molecules. We retrieved protein-protein interactions (PPIs) for combined list and built the most complete up-to-date PPI networks for presynaptic and postsynaptic compartments. We then divided this proteome up into sub-communities on the basis of network topology. We analysed three large Genome Wide Associations Studies of genetic associations with human cognitive ability, educational attainment and human diseases including autism and neurodevelopmental disorders. We find closely interacting sub-communities within the synaptic proteome that are very highly enriched for genetic associations with a range of phenotypes and disorders. These sub-communities likely indicate molecular pathways that span complex traits and disease

15:30 *Patricia Jensen*

Developmental disruption of locus coeruleus-norepinephrine signaling results in male-specific behavioral phenotypes relevant to neurodevelopmental disorders

ABSTRACT. Autism spectrum disorder (ASD) is a heterogeneous group of neurodevelopmental disorders that affects boys four times more frequently than girls. In addition to the clinically characterized deficits in social interaction and communication, a number of other conditions – including attention deficit/hyperactivity disorder,

learning disorders, and seizures – frequently co-occur with ASD. While it has been proposed that developmental dysregulation of the locus coeruleus-norepinephrine (LC-NE) system underlies some of the behavioral deficits associated with these conditions, supporting evidence is lacking. Unfortunately, current strategies aimed at testing this developmental hypothesis are restricted to manipulation of the adult LC-NE system, due to the difficulty of targeting the developing LC without affecting other central and peripheral NE neurons. To circumvent this problem, we exploited our finding that LC-NE neurons are uniquely defined by embryonic expression of the transcription factor Engrailed 1 (En1) and later expression of dopamine β-hydroxylase (Dbh), the enzyme required to convert dopamine to NE. We generated a conditional knockout allele of Dbh and crossed it with En1cre to selectively eliminate NE synthesis in LC neurons during embryonic development (LC-NE mutants). Unlike the full Dbh knockout, which is embryonic lethal, LC-NE mutants survive to adulthood, allowing us to evaluate the consequences of embryonic disruption of LC-NE on adult behavior. We subjected LC-NE mutants and littermate controls to a battery of behavioral tests to assess sociability, general activity, and learning. We found that male, but not female, LC-NE mutants exhibit reduced sociability, as well as hyperactivity, impaired contextual learning and increased incidence of seizures. Surprisingly, results from mass spectrometry revealed that only female LC-NE mutants have elevated dopamine levels in the cortex consequent to Dbh loss. These data suggest that the behavioral phenotypes observed in male mutants are likely due to loss of LC-NE, and that elevated dopamine in females may compensate for NE loss. Taken together, our data demonstrate that LC-NE mutants exhibit several behavioral deficits observed in ASD and associated disorders, providing a new experimental system to investigate how developmental dysregulation of LC-NE drives these sex-specific phenotypes.
1Neurobiology Laboratory, 2Neurobehavioral Core, National Institute of Environmental Health Sciences, National Institutes of Health, Dept. of Health and Human Services, Research Triangle Park, NC, USA. 3Mouse Behavioral Phenotyping Core, CIDD, University of North Carolina-Chapel Hill

I Evsyukova1, N Plummer1, KG Smith1, JM Strauss1,2, N Riddick3, S Moy3, JD Cushman1,2, P Jensen1

15:30-16:00 Coffee Break

16:00-17:00 Session 25: Presidential Lecture

Presidential Lecture

Dr. William Schafer

CHAIR: *Catharine Rankin*

16:00 *William Schafer*

The neuromodulatory connectomes of C. elegans

ABSTRACT. The synaptic connectome of C. elegans has been mapped completely, and efforts are ongoing to map the connectomes of other animals. However, chemical synapses represent only one of several types of signaling interactions upon which the nervous system depends. In particular, neuromodulatory interactions involving monoamines, neuropeptides, or classical neurotransmitters are widespread in all nervous systems, and these interactions often occur extrasynaptically between neurons unconnected by wired synapses. In the nematode C. elegans, it is feasible to map these neuromodulatory networks comprehensively and at a single-cell level and examine in detail how wired and wireless signaling interact in the context of the connectome. In this talk, I will describe what we have learned about the functional organisation of neuromodulatory circuitry involved in the control of behavioural states such as arousal, as well as our ongoing efforts to comprehensively map extrasynaptic connectome networks in the worm. In addition, I will discuss our identification of new ionotropic receptors for monoamines and other neuromodulators, which may represent novel targets for anti-parasitic drugs.

William Schafer, Neurobiology Division, MRC Laboratory of Molecular Biology, Cambridge CB2 0QH, UK

19:30-23:30 Banquet

Banquet Dynamic Earth
