Date: Monday, 22/May/2023

9:00am — Entrance of HBB (11 on campus map)

Meeting Registration
Location: Entrance of HBB (11 on campus map)

10:00am — PC suite AMB-G035 in the School of Psychology (4 on campus map)

Educational Workshop: Functional interpretation of GWAS data
Location: PC suite AMB-G035 in the School of Psychology (4 on campus map)
Session Chair: **Derek Morris**

12:00pm — Foyer of HBB (11 on campus map)

Lunch
Location: Foyer of HBB (11 on campus map)

1:00pm — The View, Aras na MacLeinn (10 on campus map)

Trainee Workshop
Location: The View, Aras na MacLeinn (10 on campus map)
Session Chair: **Kristin Scaplen**

3:00pm

Afternoon Break

3:30pm — The View, Aras na MacLeinn (10 on campus map)

Resume Trainee Workshop
Location: The View, Aras na MacLeinn (10 on campus map)
Session Chair: **Kristin Scaplen**

5:00pm — Large Lecture Theatre in HBB (11 on campus map)

Welcome and Opening
Location: Large Lecture Theatre in HBB (11 on campus map)

5:15pm — Large Lecture Theatre in HBB (11 on campus map)

Keynote Address: Professor Eilís Dowd
Location: Large Lecture Theatre in HBB (11 on campus map)
Session Chair: **Derek Morris**

Cellular Brain Repair for Parkinson's Disease: is the Answer in the (Biomaterial) Matrix?

5:45pm — Large Lecture Theatre in HBB (11 on campus map)

Flim and Discussion: Screening of "Feats of Modest Valour" and Panel Discussion
Location: Large Lecture Theatre in HBB (11 on campus map)

7:00pm — Sult Bar (D on campus map)

Welcome Barbecue
Location: Sult Bar (D on campus map)

Date: Tuesday, 23/May/2023

8:30am — Entrance of HBB (11 on campus map)

Meeting Registration
Location: Entrance of HBB (11 on campus map)

9:00am — Large Lecture Theatre in HBB (11 on campus map)

Symposium 1: Genes, Circuits, and Environment in Chronic Pain
Location: Large Lecture Theatre in HBB (11 on campus map)
Session Chair: **Michelle Roche**

11:00am

Morning Break

11:30am — Large Lecture Theatre in HBB (11 on campus map)

Selected Talks I
Location: Large Lecture Theatre in HBB (11 on campus map)
Session Chair: **Paul Meyer**
Session Chair: **Atoosa Samani**

1:00pm — An Bhialann Restaurant (A on campus map)

Lunch
Location: An Bhialann Restaurant (A on campus map)

2:00pm — Large Lecture Theatre in HBB (11 on campus map)

Symposium 2: Investigating Genetic Relationships in Psychiatry: A Circadian and Sleep Timing Focus
Location: Large Lecture Theatre in HBB (11 on campus map)
Session Chair: **Laura Fahey**
Session Chair: **Lorna Lopez**

4:00pm

Afternoon Break

4:30pm

Early Career Achievement Award: Dr. Sandra Sanchez-Roige
Location: Large Lecture Theatre in HBB (11 on campus map)
Session Chair: **Dai Stephens**

Large Lecture Theatre in HBB (11 on campus map)	CADM2 is implicated in impulsive personality and numerous other traits by genome- and phenome-wide association studies in humans and mice
5:30pm **Seminar Room in HBB (11 on campus map)**	**Poster Session I** Location: **Seminar Room in HBB (11 on campus map)**

Date: Wednesday, 24/May/2023

8:30am **Entrance of HBB (11 on campus map)**	**Meeting Registration** Location: **Entrance of HBB (11 on campus map)**
9:00am **Large Lecture Theatre in HBB (11 on campus map)**	**Symposium 3: Impact of Environmental Exposures Across Species and Lifespan: Untangling complex regulation of genes and behavior** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Kristin Hamre** Session Chair: **Megan Mulligan**
11:00am	**Morning Break**
11:30am **Large Lecture Theatre in HBB (11 on campus map)**	**Selected Talks 2** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Sam Gottlieb** Session Chair: **Kristin Scaplen**
1:00pm **An Bhialann Restaurant (A on campus map)**	**Lunch** Location: **An Bhialann Restaurant (A on campus map)**
2:00pm **Large Lecture Theatre in HBB (11 on campus map)**	**Symposium 4: Investigating convergent biological mechanisms across neuropsychiatric disorders** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Chang-Hui Pak**
4:00pm	**Afternoon Break**
4:30pm **Large Lecture Theatre in HBB (11 on campus map)**	**Presidential Speaker: Dr. Jamaji Nwanaji-Enwerem** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Judith Grisel** Environments and Human Heath: Underscoring The Importance of Behavior.
5:30pm **Seminar Room in HBB (11 on campus map)**	**Poster Session 2** Location: **Seminar Room in HBB (11 on campus map)**

Date: Thursday, 25/May/2023

8:30am **Entrance of HBB (11 on campus map)**	**Meeting Registration** Location: **Entrance of HBB (11 on campus map)**
9:00am **Large Lecture Theatre in HBB (11 on campus map)**	**Symposium 5: The role of inflammation in psychosis** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Declan McKernan** Session Chair: **Sinead King**
11:00am	**Morning Break**
11:30am **Large Lecture Theatre in HBB (11 on campus map)**	**Selected Talks 3** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Dara Cannon** Session Chair: **William Lynch**
1:00pm **Foyer of HBB (11 on campus map)**	**Lunch** Location: **Foyer of HBB (11 on campus map)**
1:45pm **Large Lecture Theatre in HBB (11 on campus map)**	**Business Meeting** Location: **Large Lecture Theatre in HBB (11 on campus map)**
2:45pm **Large Lecture Theatre in HBB (11 on campus map)**	**Outstanding Travel Awardees** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Helen Kamens**

4:15pm	**Afternoon Break**
4:45pm **Large Lecture Theatre in HBB (11 on campus map)**	**Distinguished Investigator Award: Professor Catharine Rankin** Location: **Large Lecture Theatre in HBB (11 on campus map)** Session Chair: **Karla Kaun** From simplicity to complexity- the importance of thorough behavioural analyses to the study of neurogenetics
7:30pm **The Dean Hotel**	**Banquet** Location: **The Dean Hotel**

Presentations

Keynote Address: Professor Eilís Dowd

Time: Monday, 22/May/2023: 5:15pm · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Derek Morris

Cellular Brain Repair for Parkinson's Disease: is the Answer in the (Biomaterial) Matrix?

Cellular Brain Repair for Parkinson's Disease:
is the Answer in the (Biomaterial) Matrix?
Professor Eilís Dowd
Pharmacology & Therapeutics and Galway Neuroscience Centre,
University of Galway, Ireland

Cell-based brain repair is a promising therapeutic option for Parkinson's disease whereby the nigrostriatal dopaminergic neurons that have degenerated over the course of the disease are replaced by transplantation of healthy neurons into the brain. This provides long-term reconstruction of the dopaminergic input to the striatum, therefore restoring motor ability to patients. Although the historical source of cells for transplantation has been fetal tissue after elective abortions, the field has now moved towards stem cell sources, including induced pluripotent stem cells (iPSCs). However, this approach continues to be hampered by poor transplant maturation (into dopaminergic neurons) *in situ* in the brain with <1.5% of transplanted cells maturing into dopaminergic neurons in one high-profile iPSC transplant study in primates. Thus, although stem cell-based cell replacement therapies have already started clinical testing (Kyoto Trial: UMIN000033564; BlueRock Trial: NCT04802733; STEM-PD: NCT05635409), it is imperative to continue rigorous preclinical studies to identify methods to improve their outcome to maximize their reparative/reconstructive potential. In this context, we have recently demonstrated that one method may be incorporation of biomaterials into the transplantation process.

In this talk, we will present our recent data demonstrating that dopaminergic cell replacement in the Parkinsonian rodent brain, using both fetal and IPSC-derived cells, is enhanced when the cells are transplanted in a neurotrophin-enriched, immune-shielding collagen hydrogel. The hydrogel provides the transplanted neurons with a physical scaffold for cell-matrix adhesion, a neurotrophin reservoir for sustained neurotrophin exposure after transplantation, and shielding from the deleterious effects of the host innate immune response. Together these beneficial mechanisms allow for a dramatic (up to 16 fold) improvement in dopaminergic maturation of the transplants *in situ* in the Parkinsonian brain.

Overall, this work suggests that the clinical transplant field should move towards the incorporation of biomaterials, such as neurotrophin-enriched collagen hydrogels, into future clinical trials using primary and/or iPSC derived neurons. Improving the safety and efficacy of such approaches, using this minimally invasive and injectable hydrogel that offers a neuroprotective and immune shielding microenvironment to the transplanted cells, could dramatically improve the reparative capacity of cell therapy for PD, and ultimately lead to an improved therapy for patients.

Acknowledgements: Our research in this field is supported by grants from the Michael J Fox Foundation for Parkinson's Research (Grant Number: 17244), Science Foundation Ireland (Grant Numbers: 19/FFP/6554, 13/RC/2073_P2) and the European Union Horizon 2020 Programme ((H2020-MSCA-ITN-2015) under the Marie Sklodowska-Curie Innovative Training Networks and Grant Agreement No. 676408).

Cellular Brain Repair for Parkinson's Disease: is the Answer in the (Biomaterial) Matrix?

Eilis Dowd
University of Galway

Professor Eilís Dowd

Cell-based brain repair is a promising therapeutic option for Parkinson's disease whereby the nigrostriatal dopaminergic neurons that have degenerated over the course of the disease are replaced by transplantation of healthy neurons into the brain. This provides long-term reconstruction of the dopaminergic input to the striatum, therefore restoring motor ability to patients. Although the historical source of cells for transplantation has been fetal tissue after elective abortions, the field has now moved towards stem cell sources, including induced pluripotent stem cells (iPSCs). However, this approach continues to be hampered by poor transplant maturation (into dopaminergic neurons) in situ in the brain with <1.5% of transplanted cells maturing into dopaminergic neurons in one high-profile iPSC transplant study in primates. Thus, although stem cell-based cell replacement therapies have already started clinical testing (Kyoto Trial: UMIN000033564; BlueRock Trial: NCT04802733; STEM-PD: NCT05635409), it is imperative to continue rigorous preclinical studies to identify methods to improve their outcome to maximize their reparative/reconstructive potential. In this context, we have recently demonstrated that one method may be incorporation of biomaterials into the transplantation process.

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Overall, this work suggests that the clinical transplant field should move towards the incorporation of biomaterials, such as neurotrophin-enriched collagen hydrogels, into future clinical trials using primary and/or iPSC derived neurons. Improving the safety

and efficacy of such approaches, using this minimally invasive and injectable hydrogel that offers a neuroprotective and immune shielding microenvironment to the transplanted cells, could dramatically improve the reparative capacity of cell therapy for PD, and ultimately lead to an improved therapy for patients.

Pharmacology & Therapeutics and Galway Neuroscience Centre,
University of Galway, Ireland

Acknowledgements: Our research in this field is supported by grants from the Michael J Fox Foundation for Parkinson's Research (Grant Number: 17244), Science Foundation Ireland (Grant Numbers: 19/FFP/6554, 13/RC/2073_P2) and the European Union Horizon 2020 Programme ((H2020-MSCA-ITN-2015) under the Marie Sklodowska-Curie Innovative Training Networks and Grant Agreement No. 676408).

Symposium 1: Genes, Circuits, and Environment in Chronic Pain

Time: Tuesday, 23/May/2023: 9:00am · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Michelle Roche

Genes, Circuits, and Environment in Chronic Pain

Michelle Roche
University of Galway

Symposium Chair: Michelle Roche

Symposium Abstract:

Chronic pain is a leading global health issue affecting up to 1 in 5 of the adult population. Current analgesic treatments are sub-optimal, with limited efficacy, unwanted side-effects and high misuse potential. This symposium will bring together early-career and established neuroscientists to discuss the role of novel systems and targets in mediating and modulating pain. The researchers will present data examining the role of genes, neural circuitries, the microbiome and endocannabinoid systems in the pathophysiology of chronic pain, the identification of biomarkers for chronic pain and novel therapeutic targets. This symposium will incorporate and compare data generated across a diverse range of preclinical models and clinical patient populations and examine the impact of stress and sex/gender.

RNA binding protein Rbfox1 has an evolutionary conserved role in regulating normal nociception and pain processing

Olga Baron
University College Dublin

Roach F.[1,2], Oggero S.[2], Goodwin G.[2], Phillimore L.[2], Ji J., Tychi N.[2], Neely G.[3], Baron O[1,2].

Nociceptive escape responses to noxious thermal and mechanical stimuli are widely conserved across metazoan species, including the fruit fly. *Drosophila* larvae and adults possess peripheral somatosensory neurons, which resemble vertebrate nociceptors both structurally and functionally. Studies in larval and adult models demonstrated that the peripheral nociceptors exhibit chronic sensitization following epithelial and nerve injury. About 70% of disease genes are conserved in flies and therefore encourage use of *Drosophila* genetics for identification of molecular mechanisms important for chronic pain.

Here, we discuss evidence that RNA binding protein Rbfox1 has an evolutionary conserved role in regulating normal nociception and sensitisation of the nociceptive system. Significant number of target genes which are regulated by Rbfox1 are also associated with chronic pain and abnormal nociception. Additionally, there is a considerable genetic and functional evidence for Rbfox1 involvement in a number of musculoskeletal conditions and therefore warrants further inquiry into its contribution to pain mechanisms.

We have developed video assisted behavioural assays that allow automated and unbiased quantification of stereotypic escape behaviours in Drosophila. Using this assays in combination with traditional sensory testing analyses in genetically modified mice we provide robust evidence that Rbfox1 has an evolutionary conserved role in regulating normal behavioural response to noxious stimulus. Additionally, we employed translational reporter tools to demonstrate that Rbfox1 activity adapts to noxious stimulation and is upregulated following sensitisation in fly nociceptors. Indeed, overexpressing Rbfox1 in Drosophila nociceptors prevents injury induced increase of heat evoked jump behaviour. We propose that Rbfox1 is a critical contributor to the adaptation of the nociceptive circuit in the process of pain resolution following injury.

1 UCD Conway Institute, University College Dublin, Ireland; 2 Wolfson Centre for Age-Related Diseases, King's College London, UK; 3 School of Life and Environmental Sciences, University of Sydney, Australia

Investigating prefrontal control of periaqueductal grey function in rat models of pain and stress

Robert Drake
University of Bristol

Dr Robert Drake[1]

The midbrain periaqueductal grey orchestrates sensorimotor and autonomic systems to produce stereotyped coping-like behaviours in response to innate and conditioned threats. The medial prefrontal cortex exerts top-down modulation of PAG function to meet the demands required for survival, but how this executive control is dynamically altered following injury or stress is not well understood. Furthermore, injury and stress effects on mPFC function are sex differentiated providing the basis for sex-dependent vulnerability to disorders of pain and mood for which flexible coping is important. I have used a combination of opto- and chemogenetic circuit dissection, in vivo oxygen amperometry and behavioural interrogation to explore 1) how the mPFC engages PAG function in response to threat, 2) how mPFC – PAG communication is altered following pain and stress and 3) how these differ between male and female rats. In male rats, I find that mPFC – PAG projections engage endogenous pain modulation residing in the PAG to regulate pain-like behaviour during noxious stimulation or after injury but then fails at later post-injury timepoints to contribute to the full development of neuropathic hypersensitivity. How failure in the cortical control of the PAG impacts wider PAG mediated behaviours and how this differs in female animals is the focus of on-going research and preliminary findings will be discussed.

School of Physiology, Pharmacology and Neuroscience, University of Bristol, United kingdom

Funding: This work is jointly supported by: Medical Research Council & Medical Research Foundation.

Towards identification of biochemical and molecular biomarkers of chronic pain

David Finn
University of Galway

DP Finn

Chronic pain is a debilitating condition affecting ~20% of the world's population and having profound negative impacts on individuals, societies and economies. Chronic pain is difficult to treat, and is often refractory to current analgesics. Improved treatment of chronic pain would be facilitated by the development of objective clinical diagnostic and treatment strategies based on robust biomarkers. To date however, identification of clinically useful biomarkers for chronic pain has proven difficult, due in part to the complex, multi-factorial nature of the condition. Using a translational approach employing animal models of chronic pain and human patient blood sampling, we have identified a number of candidate gene biomarkers of chronic pain in recent years (e.g. *TIMP1*, *CHPT1, WLS, CASP5, CASP8, CASP9, FPR2, SH3BGRL3,* and *TMEM88*; Buckley *et al*., 2018 Mol Neurobiol 55(3):2420-2430; Islam *et al*., 2022 Neuromolecular Med 24(3):320-338; Young *et al*., 2023 Mol Neurobiol 60(3):1179-1194). Increasing evidence supports a potential role for the endogenous cannabinoid (endocannabinoid) system as a novel analgesic target, and a potential source of diagnostic or prognostic

biomarkers relevant to chronic pain. Recent data will be presented revealing changes in the endocannabinoid system in people with chronic pain (e.g. neuropathic pain and low back pain) and in preclinical animal models. These data may inform the development of novel endocannabinoid-based therapeutics and biomarkers for chronic pain conditions.

Pharmacology and Therapeutics, School of Medicine, Galway Neuroscience Centre, Centre for Pain Research, University of Galway, Ireland.

Gut Feelings: The Microbiome and Pain Disorders

Siobhain O'Mahony
University College Cork

Siobhain O'Mahony

he complex ecosystem that is the gastrointestinal microbiome (including bacteria, fungi, viruses, phage) plays essential roles in the maintenance of the healthy state of its host. A disruption to the balance of this microbiome has been implicated not only in gastrointestinal disease but also neurological disorders including chronic pain. The influence of the gut microbiome is well documented in the context of visceral pain from the gastrointestinal tract; a greater understanding is starting to emerge with regard to its impact on somatic pain. The gut microbiome is an essential source for driving immune maturation and maintaining appropriate immune response. Furthermore, the microorganisms in our gut produce metabolites, neurotransmitters, and neuromodulators which interact with their receptors to regulate peripheral and central sensitisation associated with chronic pain. Microbiota-derived mediators can also regulate neuroinflammation, which is associated with activation of microglia as well as infiltration by immune cells, known to modulate the development and maintenance of central sensitisation. Investigations are needed to determine the role of the gut microbiome in this chronic pain which may inform the development of preventative interventions as well as management strategies to improve patient outcome and mental health.

Here I will present data from both preclinical animal models and clinical populations, highlighting the importance of the gut microbiome and its products in alterations in pain responding and nociceptive processing.

University College Cork

Selected Talks I

Time: Tuesday, 23/May/2023: 11:30am · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Paul Meyer
Session Chair: Atoosa Samani

The Potential Role of lncRNA MALAT1 in Alcohol Use Disorder

Sean Farris
University of Pittsburgh

AM Baratta1, SL Plasil2, GE Homanics1,2, SP Farris1,2

Long noncoding RNA (lncRNA) are increasingly recognized as significant regulators of normal biological functions, such as transcriptional regulation and alternative splicing, as well as mediating disease processes. Originally examined in the context of cancer, the lncRNA metastasis associated lung adenocarcinoma transcript 1 (*Malat1*) has been found to be involved in inflammatory processes throughout the body, as well as a number of diseases. *Malat1* expression is elevated in the prefrontal cortex of human AUD subjects and chronically drinking mice, and single cell RNA-Seq revealed that this increased expression is observed only in astrocytes. As neuroinflammation is a common consequence of excessive drinking and is thought to drive consummatory behavior, we hypothesize that changes in *Malat1* expression impact neuroinflammatory responses to ethanol. Using CRISPR/Cas9 in primary mouse astrocyte cultures, we knocked down *Malat1* expression and performed a preliminary RNA-Seq screen to quantify changes in gene expression. Concurrently, we used a novel CRISPR approach to rapidly create *Malat1* global knockout animals and subsequently tested ethanol drinking behavior. Results from our RNA-Seq pilot indicated knockdown of *Malat1* expression in primary astrocytes led to a significant upregulation in a number of interferon-signaling related genes, including *Isg15*, *Ifit1*, *Ifit3*, *Iigp1*, and *Irf7*. Every other day two-bottle choice (EOD-2BC) drinking revealed a female specific decrease in ethanol consumption in *Malat1* knockout animals. Taken together, our results indicate that *Malat1* plays a role in the perpetuation of drinking behavior, possibly through regulation of neuroimmune responses. To further understand the interplay between *Malat1* and ethanol, we will be performing Perturb-Seq in primary astrocyte cultures and observing changes in neuroinflammatory gene expression. Our results indicate that astrocytes may play an outsized role in controlling *Malat1* dependent neuroinflammatory effects and underscore the importance of investigating lncRNAs in a glia-specific context.

1University of Pittsburgh, Center for Neuroscience, Pittsburgh, PA, 15213 USA

2University of Pittsburgh, Department of Anesthesiology & Perioperative Medicine, Pittsburgh, PA, 15261 USA

Funding: We gratefully acknowledge the support of NIH/NIAAA grants AA020889, AA10422, AA024836, and T32 NS007433-22.

Alcohol consumption during early adulthood in a preclinical mouse model of Alzheimer's disease leads to gait impairments, dysregulated circadian rhythm, alterations in tauopathy and brain-region-specific transcriptional alterations.

Nicole Maphis
University of New Mexico

NM Maphis1,2 D Furlano1,2 SA David1,2 and DN Linsenbardt1,2

Alzheimer's disease (AD) is a leading cause of cognitive dysfunction and death in the US attributable in part to the accumulation and spread of pathologically modified tau (pTau). Recently, excessive alcohol use, particularly binge drinking, has emerged as a risk factor for the development of AD. However, the neurobiological consequences underlying how excessive alcohol exposure might lead to the accumulation and/or progression of pTau and associated neurobehavioral deficits has not been fully explored. We used the binge-alcohol drinking paradigm, 'drinking-in-the-dark' (DID), in the P301S mouse model of tauopathy to test the hypothesis that excessive voluntary alcohol consumption during young adulthood would exacerbate pTau-induced alterations in behavioral decline as a consequence of the recruitment of unique neurobiological genes/gene networks. We found that excessive alcohol use in the P301S mice altered the presentation of pTau, shortened circadian rhythm, impaired right hind paw gait characteristics, and led to brain-region-specific transcriptional alterations. Of particular interest, we identified a well-characterized thyroid transport gene, Transthyretin (*Ttr*), recently found to regulate microtubule dynamics and has a strong connection to Alzheimer's, that was downregulated in the hippocampus of alcohol consuming P301S males compared with alcohol consuming male nTg littermates. These findings support alcohol consumption as a factor that interacts with pTau and pTau-associated behavioral decline as well as reveals some potential targetable neurobiological mechanisms underlying these changes.

Department of Neurosciences, New Mexico Alcohol Research Center, School of Medicine and Health Sciences Center, University of New Mexico, Albuquerque, NM 87131, USA

Funding Support: NIH/NIA/NIAAA R00AA025120-05S1, NIH K12 GM088021, P50-AA022534 (Drs. Savage & Valenzuela), the Substance Use Disorders Grand Challenge Initiative supported by the Center on Alcohol, Substance use, And Addictions (CASAA)., "This project was supported by UNM HSC- Neurosciences- Center for Brain Recovery & Repair-department incentives."

Mendelian randomisation identifies gene expression alterations associated with chronotype and neuropsychiatric disorders

Shane Crinion
University of Galway

Shane Crinion1, Lorna M. Lopez2, Derek W. Morris1

Sleep disruption is a common feature of neuropsychiatric disorders (NPDs). Chronotype (morning/evening person) is a behavioural indicator of underlying circadian rhythm. Our research focuses on these phenotypes because the evening chronotype has been linked to increased risk of NPDs (autism spectrum disorder, attention deficit hyperactivity disorder, bipolar disorder, insomnia, major depressive disorder and schizophrenia). Genome-wide association studies indicate that these phenotypes are highly polygenic with many risk variants mapping to non-coding regions and are likely to functionally affect gene expression. We used Mendelian randomisation (MR) to explore the causal role of gene expression alterations (exposure) on NPD risk and chronotype (outcome(s)). We used MR in conjunction with colocalization, a method used to test if two traits (gene expression and phenotype) are caused by a shared variant in a genomic region. One hundred and seventy-five significant causal associations were identified through MR, of which twelve passed colocalization analysis. Six of the twelve associated expression quantitative trait loci (eQTL)-gene pairs were blood-mediated and nine of the twelve were associated with schizophrenia. The analysis validated the association of several genes with different phenotypes (*RP11-890B15*-schizophrenia, *GPN3*-schizophrenia, *SNX19*-schizophrenia, *FADS2-bipolar disorder*) and identified a number of eQTLs (rs3751033, rs968567, rs4968646, rs3743138, rs7535162, rs17128077, rs11979881) not previously reported in the literature as associated with these phenotypes. Overall, MR and colocalization found evidence for causal associations that link changes in gene expression levels to NPDs and chronotype.

1 Centre for Neuroimaging, Cognition and Genomics, School of Biological and Chemical Sciences, University of Galway, University Road, Galway, Ireland;

2 Department of Biology, Maynooth University, Maynooth, Co. Kildare, Ireland

Closing the loop on Turicibacter

Jason Bubier

Jackson Laboratory

JA Bubier1, GM, Weinstock2, EJ Chesler1, Y Zhou2

Substance use disorders remain among the most poorly managed health conditions despite significant knowledge of the underlying genetic, cellular and circuit mechanisms. Renewed hope for potential microbiome-based therapeutics derives from increasing evidence that i) the gut microbiome is essential in regulating addiction-related behavior and ii) host genetics can influence gut microbiome composition. Gut microbes and the small molecules they produce may constitute useful interventions and tools for studying the process of addiction. However, a major challenge is establishing a causal relationship between microbiome/microbial metabolites and addiction-related behavior. The Diversity Outbred (DO) and Collaborative Cross (CC) mouse populations are ideal for utilizing inherent genetic and phenotypic variation to discover disease mechanisms. We found that *Turicibacter* abundance is correlated with anxiety and risk-taking behavior in DO mice and identified the gene responsible for this trait, arylsulfatase B (*Arsb*). *Arsb* mutants display developmental abnormalities and elevated excreted glycosaminoglycan (GAG) levels. We further showed that *Turicibacter* abundance, peripheral metabolite concentrations, and several behaviors differ in *Arsb* mutant mice. *Turicibacter* is known to regulate bile acid levels; consistent with these findings, we discovered profound changes in bile acid concentrations in *Arsb* mutant mice, including chenodeoxycholic acid (CDCA) and lithocholic acid (LCA). This work reveals a novel genetic means of the microbiome and metabolome regulation that impacts addiction-related behaviors.

1The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609. 2University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT, USA.

A Systematic Review and Meta-analysis on the Transcriptomic Signatures in Alcohol Use Disorder – a Translational Approach

Marion Friske

Mannheim, University

MM Friske1, EC Torrico1, AM Borruto1, MJW Haas1, F Giannone1, A-C Hade2,3, M-A Philips4, WH Sommer1, R Spanagel1

According to the WHO, 10-15% of the global population suffer from Alcohol Use Disorder (AUD). However, pharmacotherapeutic approaches are limited and still more than half of the patients experience at least one relapse during the first year of treatment. Therefore, new treatment targets are warranted. Understanding the molecular commonalities between pre-clinical models and the patient situation is of critical importance to develop new targets for successful therapy of AUD. In this translational study, we combine transcriptome-wide data from brain tissue of the post-dependent rodent model, which is well known to full-fill DSM-IV criteria of human alcohol dependence and human post-mortem brain samples. In our cross-species meta-analysis, we integrated gene expression datasets derived from 108 rodent and 380 human brain samples derived from the prefrontal cortex (PFC). In the human AUD brain, 278 genes were identified as significantly dysregulated with main enrichment in immune-regulatory and pro-oncogenic pathways, while in the rodent brain, we detected 60 differentially expressed genes that were mainly enriched in pro-oncogenic, signal transduction and inflammatory pathways. In the cross-species comparative and integrative approaches, we identified that Hsd11b1 and stress-related pathways are significantly down-regulated in both, rodent and human species. Hence, our data suggest a new mechanism to explain increased cortisol levels in AUD via impaired activity of Hsd11b1, the main enzyme for the initial step in the cortisol metabolism pathway. Since this finding seems to be conserved in brain tissue of the alcohol dependent phenotype across species, we suggest this mechanism as a new treatment target for AUD.

1Institute of Psychopharmacology, Central Institute of Mental Health, Mannheim, University of Heidelberg, Germany.

2Department of Pathological Anatomy and Forensic Medicine, University of Tartu, Estonia.

3Forensic Medical Examination Department, Estonian Forensic Science Institute, Tallinn, Estonia.

4Department of Physiology, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia.

Funding support: Financial support for this work was provided by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) with the Graduiertenkolleg GRK2350/1 to RS, TRR 265 (A05 and B02) to RS (Heinz et al., 2020), SFB1158 (B04) to RS. Also supported by the German Federal Ministry of Education and Research (BMBF), “A systems-medicine approach towards distinct and shared resilience and pathological mechanisms of substance use disorders“ (01ZX01909) (to RS), and the Ministry for Science, Research and Art of Baden-Wuerttemberg (MWK) for the 3R-Center Rhein-Neckar (to RS).

Symposium 2: Investigating Genetic Relationships in Psychiatry: A Circadian and Sleep Timing Focus

Time: Tuesday, 23/May/2023: 2:00pm · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Laura Fahey
Session Chair: Lorna Lopez

Investigating Genetic Relationships in Psychiatry: A Circadian and Sleep Timing Focus

Laura Fahey
Int Behavioural and Neural Genetics Society, United States of America

Symposium Chairs: Laura Fahey and Lorna Lopez

Symposium Abstract:

To address the most recent scientific discoveries in neuropsychiatric genetics, we have brought together a diverse group of chronobiology and genetics researchers from across the globe. Sleep problems are prevalent across all neuropsychiatric conditions. Sleep is influenced by sleep/wake homeostasis, which refers to the balance that is maintained between pressure for sleep and requirement for wakefulness, and circadian rhythms, which are regulated by an endogenous 'clock' that interacts with environmental (mainly light) and behavioural cycles to promote the occurrence of sleep at the optimal time. Both sleep/wake homeostasis and circadian rhythms have been shown to be disrupted in neuropsychiatric conditions and evidence exists that this is partly due to genetic factors. Our goal for this symposium is to discuss the genetic relationship between sleep-related phenotypes and neuropsychiatric conditions. All speakers will discuss the genetic relationship between neuropsychiatric conditions and sleep-related phenotypes with a goal to understanding their molecular pathways.

The genomic correlation and causal association between sleep and attention deficit hyperactivity disorder

Marina Carpena
Federal University of Pelotas

Marina Xavier Carpena[1], Alicia Matijasevich[2], Luciana Tovo-Rodrigues[1]

[1] Post-graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil

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Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders in childhood, with great persistence in adulthood. It is marked by a continuous pattern of inattention, hyperactivity and/or impulsivity that interferes with functioning and development but has a complex, and little-known etiology. Individuals with ADHD have shorter sleep duration, more sleep problems, and circadian dysfunctions. However, it was not yet clear whether these sleep patterns are side effects or a risk factor for ADHD. We used the novel genetic markers discovery at the genomic level for sleep phenotypes and ADHD to address this gap. The cross-trait linkage disequilibrium score regression (LDSR) estimated a positive genomic correlation between ADHD and sleep problems, but not between ADHD and chronotype. These common genetic factors may play an essential role in neural signaling pathways based on our enrichment analyses. The two-sample Mendelian randomization findings indicate a causal effect of sleep disturbances and short sleep duration on ADHD reinforcing their role as predictors of ADHD. Therefore, we highlighted that comorbidity between sleep phenotypes and ADHD may be mediated by common genetic factors that play an important role in neuronal signaling pathways, and the causal effect of sleep disturbances and short sleep duration on ADHD reinforced their role as predictors of ADHD.

Association between Pathogenic Single Nucleotide Variants (SNVs) within Core Circadian Genes and Mood Disorder Phenotypes in the UK Biobank Cohort

Amy Ferguson
University of Edinburgh

AC Ferguson 1, D Smith 1, A Millar 2, L Lyall 3

Disrupted circadian rhythms are a core component of mood disorders, and several variants in core circadian genes have been associated with these, however, previous studies have focussed on only a small number of variants and genes. This study investigates the impact of the burden of many potentially pathogenic single nucleotide variants (SNVs) in 14 core circadian genes on mood disorder traits using linked healthcare records in UK Biobank (UKB) - a large population-based study. Variants recorded to be missense-, start lost- or stop gained-variants, predicted to be functionally damaging using Ensembl Variant Effect Predictor were selected for investigation. Using whole-exome sequencing, burden scores based on the number of SNVs an individual carries were created for >200,000 UKB participants. Hospital inpatient and primary care records (ICD-10 codes and Read codes, respectively) were used to identify participants with hospital admissions and/or primary care codes related to mood disorder phenotypes. The burden scores were then used to investigate the association between potentially pathogenic variants in core circadian genes and cases of mood disorder. There was a greater proportion of variant carriers with ICD-10 "Manic episode" compared to those without ($p>0.01$), and an association between a greater variant burden score and bipolar disorder ($p>0.05$). This study suggests potentially functionally damaging variants in core circadian clock genes may have an impact on the development of mood disorders, further supporting the hypothesis for the role of circadian clock genes in mood disorders.

1Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, 2Centre for Engineering Biology, University of Edinburgh, 3School of Health and Wellbeing, University of Glasgow

Fibroblasts as an in vitro model of circadian genetic and genomic studies

Marcelo Francia
University of California, Los Angeles

Marcelo Francia1, Merel Bot2,3, Toni Boltz2, Juan de la Hoz4, Roel Ophoff2,3

Skin fibroblast cells collected from bipolar disorder (BD) patients have displayed temporal differences in the expression of core circadian genes. Given that BD is polygenic, we investigated genome-wide features of circadian genetic regulation in this in vitro model, and examined to what extent these features are associated with the genetic architecture of BD risk. To do this, we collected temporal transcriptomic data (RNA-seq) and open chromatin data (ATAC-seq) over a 48 hour period. The RNA-seq data showed that only a limited number of genes, such as *ARNTL, CRY1, PER3, NR1D2* and *TEF* display circadian patterns of expression consistently across cell cultures. The ATAC-seq data identified that distinct transcription factor families, like those with the basic helix-loop-helix motif, were associated with regions that were increasing in accessibility over time. Further evaluation of these regions using stratified linkage disequilibrium score regression (sLDSC) analysis failed to identify a significant presence of them in the known genetic

architecture of BD, and other psychiatric disorders or neurobehavioral traits in which the circadian rhythm is affected. This study characterizes the biological pathways that are activated in this in vitro circadian model, evaluating the relevance of these processes in the context of the genetic architecture of BD and other disorders, highlighting its limitations and future applications for circadian genomic studies.

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Funding Support: National Institute of Neurological Disorders And Stroke of the National Institutes of Health under Award Number T32NS048004.

Genomic approaches to investigate the relationship between circadian mechanisms and the pathophysiology of neurodevelopmental and neuropsychiatric conditions

Lorna Lopez
Maynooth University

Lorna M. Lopez1, Laura Fahey1, Cathy Wyse1

Sleep problems are extremely common in neurodevelopmental and neuropsychiatric conditions. The timing of sleep is regulated by the circadian clock, which is a molecular timing mechanism driven by transcriptional and translational feedback loops in a panel of "clock" genes. Researchers have postulated that circadian dysfunction may contribute to the sleep problems of neurodevelopmental and neuropsychiatric conditions and even have a primary role in the pathophysiology of these conditions.

Genome-wide association studies (GWAS) have identified many common genetic variants associated with neurodevelopmental and neuropsychiatric conditions, and the sleep phenotypes, insomnia and chronotype (a self-reported preference for the timing of daily activity, considered a behavourial output of the circadian clock).

Statistically significant correlations of genetic effects between numerous pairs of neurodevelopmental or neuropsychiatric and sleep phenotypes have been identified. We hypothesize that this overlapping genetic variation is enriched in certain biological pathways and we use pathway-based polygenic score analysis to identify the enriched pathways. We use summary statistics from the largest GWAS of autism, attention deficit hyperactivity disorder, schizophrenia, bipolar disorder and major depressive disorder to create multiple pathway-based polygenic scores. This is done by restricting the genetic variation for each of the five neurodevelopmental and neuropsychiatric phenotypes to various biologically relevant pathways. We compare and contrast the performances of these pathway-based polygenic scores for each phenotype, in predicting chronotype and insomnia status of nearly 500,000 samples in the UK Biobank. The results presented will give insight into the potential biological mechanisms underlying sleep disruption in each of the neurodevelopmental/neuropsychiatric conditions tested.

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Early Career Achievement Award: Dr. Sandra Sanchez-Roige

Time: Tuesday, 23/May/2023: 4:30pm · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Dai Stephens

CADM2 is implicated in impulsive personality and numerous other traits by genome- and phenome-wide association studies in humans and mice

Early Career Achievement Awardee, Sanda Sanchez-Roige CADM2 is implicated in impulsive personality and numerous other traits by genome- and phenome-wide association studies in humans and mice Sandra Sanchez-Roige (Presenter)1,2, Mariela V Jennings1, Hayley H A Thorpe3, Jazlene E Mallari1, Lieke C van der Werf1, Sevim B Bianchi1, Calvin Lee1, Travis T Mallard4, Samuel A Barnes1, Jin Yi Wu1, Amanda M Barkley-Levenson1, Ely C Boussaty1, Cedric E Snethlage1, Danielle Schafer1, Zeljana Babic1, Boyer D Winters5, Katherine E Watters6,7, Thomas Biederer6, on behalf of the 23andMe Research Team8, James Mackillop9, David N Stephens10, Sarah L Elson8, Pierre Fontanillas8, Jibran Y Khokhar3, Jared W Young1, Abraham A Palmer1,11

Impulsivity is a multidimensional heritable phenotype that broadly refers to the tendency to act prematurely and is associated with multiple forms of psychopathology, including substance use disorders. We performed genome-wide association studies (GWAS) of eight impulsive personality traits from the Barratt Impulsiveness Scale and the short UPPS-P Impulsive Personality Scale (N=123,509-133,517 23andMe research participants of European ancestry), and a measure of Drug Experimentation (N=130,684). Because these GWAS implicated the gene CADM2, we next performed single-SNP phenome-wide studies (PheWAS) of several of the implicated variants in CADM2 in a multi-ancestral 23andMe cohort (N=3,229,317, European; N=579,623, Latin American; N=199,663, African American). Finally, we produced Cadm2 mutant mice and used them to perform a Mouse-PheWAS (“MouseWAS”) by testing them with a battery of relevant behavioral tasks. In humans, impulsive personality traits showed modest chip-heritability (~6-11%), and moderate genetic correlations (rg=.20-.50) with other personality traits, and various psychiatric and medical traits. We replicated associations from earlier GWAS of these traits and found novel associations including DRD2, CRHR1, FOXP2, TCF4, PTPRF. PheWAS for CADM2 variants identified associations with 378 traits in European participants, and 47 traits in Latin American participants, replicating associations with risky behaviors, cognition and BMI, and revealing novel associations including allergies, anxiety, irritable bowel syndrome, and migraine. Our MouseWAS recapitulated some of the associations found in humans, including impulsivity, cognition, and BMI. Our results further delineate the role of CADM2 in impulsivity and numerous other psychiatric and somatic traits across ancestries and species.

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Funding Support: MVJ, SBB, YH, SSR and AAP were supported by funds from the California Tobacco-Related Disease Research Program (TRDRP; Grant Number 28IR-0070, T29KT0526 and T32IR5226). SBB was also supported by P50DA037844, SSR was also supported by NIH/NIDA DP1DA054394. JM and SSR were supported by the Brain and Behavior Foundation (grant 27676) and the Families for Borderline Personality Disorder Research (Beth and Rob Elliott) 2018 NARSAD Young Investigator Grant. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. SAB was supported by NIH/NIMH grants R01MH108653 and R21MH117518. AMBL was supported by NIH/NIAAA grant K99AA027835. TB acknowledges support by NIH/NIDA R01 DA018928. JM is supported by the Peter Boris Chair in Addictions Research. HHAT is funded through a Natural Science and Engineering Research Council PGS-D scholarship, and studies in Cohort 2 were supported by the Canadian Institutes of Health Research Project Grant (PJT-173442 to JYK).

CADM2 is implicated in impulsive personality and numerous other traits by genome- and phenome-wide association studies in humans and mice

Sandra Sanchez-Roige
UCSD Department of Psychiatry

Sandra Sanchez-Roige (Presenter)[1,2], Mariela V Jennings[1], Hayley H A Thorpe[3], Jazlene E Mallari[1], Lieke C van der Werf[1], Sevim B Bianchi[1], Calvin Lee[1], Travis T Mallard[4], Samuel A Barnes[1], Jin Yi Wu[1], Amanda M Barkley-Levenson[1], Ely C Boussaty[1], Cedric E Snethlage[1], Danielle Schafer[1], Zeljana Babic[1], Boyer D Winters[5], Katherine E Watters[6,7], Thomas Biederer[6], on behalf of the 23andMe Research Team[8], James Mackillop[9], David N Stephens[10], Sarah L Elson[8], Pierre Fontanillas[8], Jibran Y Khokhar[3], Jared W Young[1], Abraham A Palmer[1,11]

Impulsivity is a multidimensional heritable phenotype that broadly refers to the tendency to act prematurely and is associated with multiple forms of psychopathology, including substance use disorders. We performed genome-wide association studies (**GWAS**) of eight impulsive personality traits from the Barratt Impulsiveness Scale and the short UPPS-P Impulsive Personality Scale (N=123,509-133,517 23andMe research participants of European ancestry), and a measure of Drug Experimentation (N=130,684). Because these GWAS implicated the gene *CADM2*, we next performed single-SNP phenome-wide studies (**PheWAS**) of several of the implicated variants in *CADM2* in a multi-ancestral 23andMe cohort (N=3,229,317, European; N=579,623, Latin American; N=199,663, African American). Finally, we produced *Cadm2* mutant mice and used them to perform a Mouse-PheWAS (“MouseWAS”) by testing them with a battery of relevant behavioral tasks. In humans, impulsive personality traits showed modest chip-heritability (~6-11%), and moderate genetic correlations (r_g=.20-.50) with other personality traits, and various psychiatric and medical traits. We replicated associations from earlier GWAS of these traits and found novel associations including *DRD2*, *CRHR1, FOXP2, TCF4, PTPRF*. PheWAS for *CADM2* variants identified associations with 378 traits in European participants, and 47 traits in Latin American participants, replicating associations with risky behaviors, cognition and BMI, and revealing novel associations including allergies, anxiety, irritable bowel syndrome, and migraine. Our MouseWAS recapitulated some of the associations found in humans, including impulsivity, cognition, and BMI. Our results further delineate the role of *CADM2* in impulsivity and numerous other psychiatric and somatic traits across ancestries and species.

Poster Session I

Time: Tuesday, 23/May/2023: 5:30pm · *Location:* Seminar Room in HBB (11 on campus map)

Poster #1. A dopaminergic circuit for escalation of alcohol use in Drosophila

John Hernandez
Brown University

Hernandez, J.S.1, Le, N.2, Azanchi, R. 1, Glenn, E.1, and Kaun, K.R.1

Escalation of alcohol self-administration facilitates the transition from alcohol use to compulsive drinking, which is a worldwide biomedical concern. Alcohol research has largely focused on understanding the neural mechanisms underlying excessive or compulsive alcohol intake. Much less is understood of the neural substrates underlying individual differences in alcohol preference and seeking, and how escalation arises in some individuals and not others. In *Drosophila melanogaster*, the neural circuits required for encoding valence include identifiable connections, genetic and/or biochemical profiles and characterized temporal changes underlying learning, making flies an ideal model for investigating escalation of ethanol self-administration. We developed a 3-day operant paradigm to evaluate the spectrum of behaviors associated with self-administration of a pharmacologically relevant dose of volatilized ethanol. Using thermogenetic inactivation approaches, we discovered a simple 2 neuron cholinergic and dopaminergic circuit within the *Drosophila* mushroom body system which alters population ethanol preference to decrease and increase ethanol self-administration, respectively. Calcium responses in this simple circuit reflect inherent behavioral preference for volatilized ethanol, and how this preference changes with experience. Our data demonstrate a dynamic shift from circuits that form memories for both aversive and rewarding properties of alcohol, to circuits that initiate cue-induced behavioral responses and escalation of alcohol self-administration.

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Poster #2. Alterations in the oral microbiome in individuals with schizophrenia

Ailis Stevenson
Ulster University

Ailis Stevenson1, Coral R Lapsley1, Jonathon McLaughlin1, John Brady2, Andrew McDowell3, Elaine K. Murray1

Oral dysbiosis has been associated with the pathophysiology of numerous systemic diseases with underlying inflammatory components, including psychiatric disorders, with growing evidence linking the oral microbiome and schizophrenia. The aim of this study was to conduct 16S rRNA sequencing to characterise the composition and examine functional differences in the oral microbiome in individuals with schizophrenia compared to controls. Microbial DNA was extracted in duplicate from saliva samples from adults with schizophrenia (n=21) and matched healthy controls (n=25). Microbiome analysis was conducted using 16S rRNA sequencing on an Illumina MiSeq. The paired-end reads were trimmed using the DADA2 package in R (v4.2.2) and the online software package EZBioCloud was used to carry out secondary analysis, including alpha diversity, beta diversity and taxonomic and functional profiling. Subtle but significant differences in alpha and beta diversity of the salivary microbiome were observed, with clear separation of schizophrenia and healthy control cohorts into distinct clusters. Several bacterial taxa were also found to be differentially abundant in the schizophrenia cohort. In this preliminary study we have shown that the composition of the oral microbiome is associated with schizophrenia. Further studies are now warranted, particularly investigations into whether such shifts play any role in the underling aetiology of schizophrenia.

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2Western HSC Trust, Northern Ireland Clinical Research Network (Mental Health)
3NICHE, School of Biomedical Sciences, Ulster University, Cromore Road, Coleraine

Funding support: Department for Education, CHITIN

Poster #3. A genome-wide analysis of potential genetic correlates linking exploratory behaviors and sensitized responses to cocaine in heterogenous stock rats

Elizabeth Rakowski
University at Buffalo

EA Rakowski1, BM Thompson1, CP King1, AS Chitre2, O Polesskaya2, SB Flagel3, TE Robinson3, LC Solberg-Woods4, D Munro2,7, LM Saba5, H Chen6, P Mohammadi7, AA Palmer2,8, & PJ Meyer1

Several studies have suggested a link between exploratory behavior and drug sensitivity. However, few studies have examined the common genomic influences on these traits. In this genome-wide association study involving 3,228 heterogeneous stock rats, we compared several ancillary measures of exploratory behavior, including unreinforced nose-poking behavior during a sensory reinforcement test, patch-switching during a patch-depletion procedure, inter-trial interval responses during a Pavlovian conditioned approach (PavCA) test, and spontaneous locomotion (including rearing) in a novel environment. We then measured genotypic and phenotypic relationships between these behaviors and drug sensitivity, defined as the initial and sensitized locomotor responses to cocaine. We found that the locomotor response to cocaine was genetically correlated with other exploratory behaviors, including inter-trial intervals during PavCA paradigm and nose-poking during a light reinforcement test. We found common loci on chromosome 10 that influenced these phenotypes, and used RNA sequencing to determine whether these regions influenced transcription of specific genes in the brain. For example, angiotensin I-converting enzyme expression in the orbitofrontal cortex and corticotropin-releasing hormone receptor I expression in the infralimbic cortex and lateral habenula were influenced by these loci on chromosome 10. Further, the initial locomotor response to cocaine was moderately genetically correlated with exploratory rearing in a novel environment and patch-switching, and influenced by similar loci on chromosome 18. Future studies will include functional analyses of candidate genes for their roles in substance use disorder and related behaviors.

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Poster #4. Cell-selective GSK3B overexpression in medial prefrontal cortex produces sex-specific changes in ethanol self-administration, anxiety-like behavior, and working memory

Sam Gottlieb
Virginia Commonwealth University

S Gottlieb[1,2,3], Z Tatom[1,3], and MF Miles[1,2,3]

Glycogen synthase kinase 3 beta (*Gsk3b*) is central in a gene network regulated by ethanol in mouse medial prefrontal cortex (mPFC). GSK3B abundance/activity modulations regulate ethanol consumption, suggesting GSK3B could be a target in treating alcohol use disorder. However, the critical cell type in this ethanol response is not yet known, nor have sex differences in GSK3B modulations been fully investigated. Here we report results of GSK3B overexpression selectively in CamKIIa^{+} mPFC cells on multiple behaviors.

Mice underwent viral stereotaxic injections to overexpress GSK3B in mPFC CamKIIa^{+} cells or a control virus (n=4-6/sex/virus). We assayed working memory using a 5min delay novel-object recognition test (NOR), basal anxiety-like behavior via light/dark box (LDB), 5-weeks 2-bottle choice, intermittent ethanol access to measure ethanol consumption and preference, withdrawal-induced anxiety-like behavior 24hrs after last ethanol access, and taste preference for saccharin (1.2mM) and quinine (100uM). Location of injections and deletion/overexpression was validated via immunofluorescence.

In initial results, GSK3B overexpression produced a significant sex*genotype interaction in NOR (p=0.018), percent distance traveled in the light during LDB (p=0.025), 24hr ethanol consumption (p=0.040), and 2hr and 24hr ethanol preference (p=0.019; p=0.007 respectively). Extension to fully statistically powered studies (n=15/sex/virus) are currently underway.

GSK3B is a promising target for treatment of alcohol use disorder as inhibition decreases ethanol self-administration. However, sufficient preclinical analysis requires full evaluation of GSK3B-modulated behaviors in both sexes. These experiments showed CaMKIIa^{+} cells to be critical in the GSK3B-ethanol pathway, as well as revealed sex-specific responses to overexpression.

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Funding Support: NIAAA grants P50AA022537, R01AA027581, F31AA030216.

Poster #5. cFos induction in RMTg afferents following chronic ethanol exposure provides insight into circuit mechanisms underlying affective and somatic symptoms of withdrawal

Hyerim Yang
University of Illinois at Chicago

H. Yang, J.R. Sanchez, E.J. Glover

Individuals with AUD often struggle to maintain sobriety due to withdrawal symptoms that emerge during early abstinence. Previous work from our lab revealed putative hyperactivity in the rostromedial tegmental nucleus (RMTg) of rats withdrawn from chronic intermittent ethanol (CIE) exposure and showed that pharmacological inhibition of the RMTg attenuates withdrawal-induced anxiety-like behavior. However, the precise neural circuits that drive this effect are unknown. To explore this, Long Evans rats were injected with the retrograde tracer, cholera toxin B (CtB), into the RMTg and rendered dependent. Rats were euthanized during acute withdrawal and tissue labeled for CtB and cFos using standard immunohistochemistry. cFos expression was compared between AIR and CIE exposed rats in brain regions with significant CtB cell body labeling. Quantification revealed a significant withdrawal-induced increase in cFos expression in CtB-labeled neurons within the lateral habenula (LHb;*p=0.029) and hypothalamus (Hyp;*p=0.013) but not the medial prefrontal cortex or periaqueductal gray (p>0.05). Because previous work implicates both the RMTg and LHb in pain regulation and decision making, we investigated whether withdrawal-induced changes in these behaviors followed a similar time course to cFos induction. Indeed, increased mechanical pain sensitivity was observed during acute withdrawal (p=0.018). In addition, withdrawn rats exhibited a significant increase in sensitivity to delayed punishment compared to controls (p<0.001). Together, these data suggest that LHb and/or Hyp inputs to the RMTg may play a role in symptoms of withdrawal including hyperalgesia and cognitive deficits. Future work will explore whether selective manipulation of these circuits alter withdrawal-induced changes in behavior.

Center for Alcohol Research in Epigenetics, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, 60612, USA

Poster #6. Characterization of Alcohol Behaviors and Food Metabolism in a Mouse Model of GCKR Human SNP rs1260326 (P446L)

Erika Mehrhoff
University of Colorado Boulder

Erika A Mehrhoff[1,2], Myra Bower[1,2], Logan Bunch[1], Nevin Fowler[1], Emma Yang[1], Garrison Verner[1], Caroline Aki[1], Luke Hendricks[3], Matt Branney[1], Harriet Lee[1], Anna Funke[1], Darleen Sandoval[4], Marissa A Ehringer[1,2]

Multiple large Genome Wide Association Studies (GWAS) of alcohol behaviors identified a non-synonymous single nucleotide polymorphism (SNP) in the human gene for the glucokinase regulatory protein (*GCKR*). SNP rs1260326 corresponds to an amino acid change at position 446 from Proline to Leucine (P446L), where the P allele is associated with increased levels of alcohol consumption (“risk” allele). This SNP is also associated with metabolic diseases such as nonalcoholic fatty liver disease and type 2 diabetes. An initial characterization of *Gckr* 446P and 446L mice showed that female PP and PL mice voluntarily consume and prefer alcohol compared to the female LL mice in two-bottle choice, consistent with what has been seen in human genetic studies. We have tested initial alcohol sensitivity, acute functional tolerance, and rapid tolerance measures within these *Gckr* 446P and 446L mice, utilizing the stationary dowel test across two days of testing. Preliminary results indicate the LL mice are less sensitive to the initial effects of alcohol on day one in both sexes. All animals display rapid tolerance on the second day of testing, with no apparent differences due to genotype or sex. Basic metabolic phenotyping of these animals found that female PP mice on a normal diet displayed higher fat mass, and on a high-fat diet they displayed greater hepatic triglyceride levels compared to female LL mice. Additional studies are needed to further characterize additional alcohol behaviors, including chronic tolerance, and further metabolic measures, including glucose handling and lipid tolerance.

[1] Department of Integrative Physiology, University of Colorado Boulder; [2] Institute for Behavioral Genetics, University of Colorado Boulder; [3] Asian Languages and Civilizations, University of Colorado Boulder; [4] Department of Pediatrics, University of Colorado Anschutz Medical Campus

Supported by R03 AA026733.

Poster #7. Characterization of the gut microbiome and oxycodone use disorder phenotypes in select rat strains of the Hybrid Rat Diversity Panel

Eamonn Duffy

University of Colorado Boulder

Eamonn Duffy2,4, Luanne Hale1, Jonathan Ward1, Kyle Brown1, Andrew Kwilasz1, Daniel Frank5, Laura Saba2,3,Ryan Bachtell1,2, Marissa A. Ehringer2,4

Opioid Use Disorder (OUD) is an ongoing worldwide public health concern. Little work has addressed how genetic background and the gut microbiome contribute to OUD. Here, we present findings from a behavioral phenotyping protocol using several inbred strains from the Hybrid Rat Diversity Panel (HRDP). We use a self-administration paradigm to measure acquisition of oxycodone intake, motivation to obtain oxycodone, and progression to compulsive oxycodone use. Prior to and following the self-administration period, we perform a modified “up-down” von Frey procedure to assess mechanical sensitivity and the tail immersion test to examine thermal sensitivity and opioid analgesia. At these timepoints, we also collect gut microbiome samples and perform 16S rRNA sequencing to assess how chronic oxycodone exposure may alter the gut microbiome. We observed strain differences in the initial mechanical and thermal sensitivity phenotypes, and estimated the broad-sense heritability of these measures to range from h^2 = 0.15-0.38. All strains acquired self-administration, and we observed strain and sex differences in the pattern of acquisition and escalation. Furthermore, we observed strain differences in gut microbiome composition prior to oxycodone self-administration, indicating that host genetics may be an important determinant. Chronic oxycodone administration also impacted gut microbiome diversity and composition in a strain-specific manner. Following self-administration, oxycodone-administering WKY/NCrl rats displayed greater alpha-diversity than the saline-administering counterparts. Our results suggest that the gut microbiome is shaped by both host genetics and chronic oxycodone exposure.

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5 Department of Medicine, Division of Infectious Diseases, University of Colorado Anschutz Medical Campus

Funding Support: NIDA U01 DA051937.

Poster #8. Determining the impact of offspring genetic diversity on maternal care and differential susceptibility to Chd8 haploinsufficiency

Manal Tabbaa
Saban Research Institute

Manal Tabbaa1,2, Pat Levitt1,2

Maternal-offspring interactions are dyadic and influenced by the genetics and behavior of the mother and offspring. Variability in these interactions may contribute to differential susceptibility to neurodevelopmental disorder risk in the offspring. However, the significance of maternal-offspring interactions in neurodevelopmental disorders are typically studied in single inbred strains which fail to replicate heterogeneity in the early social environment that exists in genetically diverse populations. To examine how the genetic diversity of offspring impacts maternal-offspring interactions in a mouse model of autism spectrum disorder, C57B/6J (B6) dams, heterozygous for the high-confidence autism risk gene, *Chd8* (*Chd8*$^{+/-}$), were paired with sires from 15 collaborative cross (CC) genetic reference panel strains to produce genetically diverse F1 B6-CC male and female wild-type or *Chd8*$^{+/-}$ littermates. Sires were removed prior to litter births. Litters (N=5-11 litters/strain) were observed for maternal and pup behaviors from the day of birth to weaning by a researcher blind to strain. A subset of mice were tested for social, anxiety-like, and cognitive traits in adulthood. Preliminary analyses reveal that total maternal care differed across offspring strain depending on the trait measured. The timing of pup developmental milestones, including leaving the nest for the first time, also varied across offspring strain. In adulthood, genetic background regulated differential susceptibility to complex traits due to *Chd8*$^{+/-}$, and ongoing analyses are testing the contribution of variability in maternal care to adult trait susceptibility. Determining the impact of offspring genetic background on maternal care provides an important foundation for interpreting adult outcomes and determining mechanisms.

1Children’s Hospital Los Angeles, The Saban Research Institute; Los Angeles, California.

2University of Southern California; Los Angeles, California.

Funding support: National Institute of Mental Health R21MH118685, National Science Foundation Postdoctoral Research Fellowship in Biology DBI 2011039, Saban Research Institute Research Career Development Fellowship, Simms/Mann Chair in Developmental Neurogenetics.

Poster #9. Assessing effects of tricaine-induced anesthesia in zebrafish larvae via live imaging of brain neuronal activity

Nils Ohnesorge
German Federal Institute for Risk Assessment

N Ohnesorge[1], J Wilzopolski[1], M Steinfath[1], L Lewejohann[1,2], S Banneke[1], C Heinl[1]

Rapid and effective anesthesia is the key to avoid pain in animal experiments as required by European law. The most commonly used substance for induction of anesthesia in zebrafish is tricaine (MS-222™). When properly prepared and dosed, tricaine causes rapid loss of mobility, equilibrium, and response to touch. These signs are interpreted as a stage of deep anesthesia, but the effects on the central nervous system have not yet been convincingly demonstrated.

To investigate the effects of tricaine on the central nervous system, we used 4 days post fertilization (dpf) transgenic zebrafish larvae expressing the fluorescent calcium sensor GCAMP6s in all neurons, allowing monitoring and quantification of neuronal activity. After treating larvae with the commonly used dose of 168 mg/L tricaine a rapid loss of neuronal activity was observed in the forebrain, visualized via confocal microscopy. In contrast, only minor effects were observed in the midbrain and hindbrain and became apparent only after several minutes.

In conclusion, we found differences in the sensitivity to tricaine between the different larval brain areas. The effects on the central nervous system are indicative of anesthetic function and are consistent with behavioral observations. However, because of the weak and slow effects on large brain areas, a longer incubation period or higher concentrations might be beneficial to achieve deep anesthesia.

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Virtual Poster. Atomoxetine reduces audiogenic fit severity

Inga Poletaeva
Moscow State University

https://ibangs.memberclicks.net/assets/documents/Poster%20Poletaeva%20et%20al.pdf

II Poletaeva 1, NM Surina 1, Fedotova IB 1, OV Perepelkina 1.

Rodent audiogenic seizures (AS) (clonic-tonic convulsions in response to loud sound) epilepsy is the well-known phenomenon which is the particular case of the refractory epilepsy. The morphological substrate of AS is well described, including brain stem structures with subsequent involvement of midbrain and spinal motor neurons. The data on neurochemical traits in AS-prone rat strains (bred independently) indicate the neurotransmitter misbalance in the background and as the response to AS. The data point as well to the multiple changes in numerous neurotransmitter systems which means probably that this type of brain pathology emerges during early ontogeny. The polygenic determination of this trait was established several decades ago. Brain catecholamine (namely, gene cascades of their release and inactivation) play the important role in AS expression, the brain noradrenergic (NA) machinery being among them. The data presented the first attempt to change the brain NA level by means of single injection of atomoxetine (15 and 30 mg/kg), the drug which inhibits the NA reuptake. In male rats of highly AS-prone KM strain, atomoxetine decreased slightly the AS latency and intensity, while the similar treatment of 101/HY strain male mice (highly AS-prone) resulted in suppression of AS, and in control group the sound exposure resulted in death of 55% of animals ($p<0.01$).

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Funding: Supported by Russian Scientific Foundation, grant N 23-25-00042

Poster #10. Behavioral assessment of cognitive models of schizophrenia using novel mouse CANTAB-like test battery

Konstantin Andrianov
Haifa University

Konstantin Andrianov, Jenan Azaizah, Inna Gaisler-Salomon

Cognition is among the first domains to be affected in schizophrenia, and can predict the onset of psychosis. Measuring cognitive changes in schizophrenia is a complex process, which often involves a battery of multiple tests, where individual performance is compared to the average performance of the healthy population. Animal models are often used to probe into mechanisms of cognitive dysfunction. However, animal models of cognitive dysfunction in schizophrenia and other disorders usually focus on a single cognitive domain using a limited number of cognitive assays. In addition, behavioral analysis is performed at the group level without reference to individual variability. In the present study, we designed a battery of cognitive tests equivalent to the schizophrenia relevant human CANTAB battery. This battery included multiple relevant assays per animal such as learning, memory, social behavior tests, problem solving and extra dimensional set shifting. To assess the relevance of the battery to schizophrenia research, we tested glutamate dehydrogenase (Glud1)-deficient mice, previously shown to mimic schizophrenia-like phenotypes (Lander et al. 2019). The performance of each animal in each assay was compared to the average performance of a control group, and the classification of animals into levels of cognitive vulnerability was based on abnormal performance in several assays. Animals were categorized into three groups: High-, Average- or Low-cognitive performers. We found an unequal distribution of cognitive performance in the different genotypes tested. This indicates that the novel mouse CANTAB-like battery may be a useful tool for the assessment of cognitive abnormalities in schizophrenia.

Department of psychology, “Molecular basis of psychopathology” Lab , University of Haifa, Haifa Israel,

Poster #11. Behavioural characterisation of an incisional wound model, and investigation of associated alterations in the endocannabinoid system

Catherine Healy
University of Galway

Catherine R Healy1,2,3,4, Maria C Redmond1,2,3,4,Mehnaz I Ferdousi**1**,2,3, Georgina Gethin4,5,6, Abhay Pandit4, David P. Finn1,2,3,4

Wound-associated pain represents a significant unmet clinical need. The endocannabinoid system (ECS) is involved in the modulation of nociception and is a potential therapeutic target for improved management of would-associated pain. This study characterised pain-related behaviour in the rat back hairy skin incision model, and investigated ECS alterations in key brain regions. Male and female SD rats (210-320g, n=4-5/group) underwent dorsum incision or sham surgery. Mechanical hypersensitivity (MH) was assessed at baseline and up to post-surgery day (PSD) 33. Levels of endocannabinoids AEA and 2-AG, and *N*-acylethanolamines (NAEs) PEA and OEA were analysed in PFC, PAG, and RVM via LC-MS/MS. qRT-PCR assessed expression of mRNA encoding CB_1, CB_2, MGL and FAAH in the PAG. MH was observed in male incision rats vs male sham ($p<0.05$). There were no differences in mechanical withdrawal thresholds between female incision rats and female sham. There was significantly higher levels of 2-AG in male incision rats vs male sham in PFC and PAG ($p<0.05$). There was significantly higher expression of mRNA encoding CB_1, CB_2 and FAAH in the PAG of male incision rats vs male sham ($p< 0.05$). There was significantly lower expression of mRNA encoding CB_2 in the PAG of female incision vs female sham ($p<0.05$). These results suggest that only male rats show mechanical hypersensitivity following dorsum incision. The alteration in ECS in key brain regions related to pain modulation in male back incision rats could indicate sexually dimorphic, incision-induced changes, and could have implications for ECS signalling following incisional wound injury.

1 Pharmacology and Therapeutics, School of Medicine, 2 Galway Neuroscience Centre, 3 Centre for Pain Research, University of Galway, 4 CÚRAM, SFI Research Centre for Medical Devices, 5 School of Nursing and Midwifery, 6 Alliance for Research and Innovation in Wounds, University of Galway

Poster #12. Beta-Endorphin Reduces Ethanol-Induced Ataxia in Mice

Samuel Stea
Bucknell University

SG Stea1, JE Grisel1,2

Beta-Endorphin (β-E) is an opioid neuropeptide associated with ethanol (EtOH) effects. EtOH oxidation into acetaldehyde, facilitated by brain catalase, leads to β-E release. Acetaldehyde and catalase have been shown to regulate effects of EtOH, including psychomotor arousal and sedation, however the role of β-E in these behaviors has not previously been explored. We examined the influence of β-E on ataxic effects of EtOH using adult male and female wild-type C57BL/6J and β-E deficient B6.129S2-*Pomc*^{tm1Low}/J mice in a parallel rod floor apparatus following either 0.75 or 2.0g/kg EtOH. Fifteen min after intraperitoneal injection, we recorded foot slips, distance traveled, slips per distance, first instance of immobility and total time spent off-balance (lying on the floor) for 15 min and collected blood for analysis of EtOH concentration 60 min after injection. Overall, β-E deficient subjects were more ataxic: they slipped more than twice as often at the lower dose, and were almost three times more likely to be immobile at the higher dose. The influence of β-E depended on sex, in that male β-E deficient mice were especially impaired. Blood EtOH concentrations did not differ between groups, indicating that the behavioral differences reflect differential sensitivity to the drug. These results suggest that β-E, similar to acetaldehyde and brain catalase, regulates the sedative effects of EtOH, and does so in a sex-dependent manner. Together these

findings further implicate β-E in sex disparities in the sensitivity and response to EtOH, and may help inform targeted treatments for AUDs.

1Neuroscience Program, 2Department of Psychology, Bucknell University, Lewisburg, Pennsylvania, United States of America

Funding Support: N/A

Poster #13. Biomaterial enhanced brain repair in Parkinsonian rats: an early comparison between cyclosporine immunosuppressed Sprague Dawley rats and athymic nude rats.

Giulia Comini
University of Galway

1Giulia Comini, 1Sarah Jarrin, 3Rachel Kelly, 1Tommy Patton, 1Kaushik Narasimhan, 2Abhay Pandit, 4Nicola Drummond, 4Tilo Kunath and 1Eilis Dowd

Recent studies in our group have shown that the survival and differentiation of iPSC derived dopaminergic progenitors (iPSC-DAPs) were dramatically improved when these were encapsulated in a neurotrophins enriched collagen hydrogel previous to transplantation in the Parkinsonian rat brain. However, the beneficial effect of the collagen hydrogel was observed in athymic nude rats but not in cyclosporine immunosuppressed Sprague Dawley rats. Therefore this study had two aims: determine the mechanism underlying the beneficial effect of the enriched collagen hydrogel and understand the differences between athymic nude rats and cyclosporine immunosuppressed Sprague Dawley rats which prevented the beneficial effect to manifest in the latter. These were assessed with two studies: one in each strain. Rats received unilateral 6-hydroxydopamine lesion followed by unilateral intra-striatal transplantation of iPSC-DAPs either alone, with neurotrophins or encapsulated in a collagen hydrogel with or without neurotrophins. Rats were euthanized at 1, 4 and 7 days post-transplantation. In both strains of rats, the hydrogel was able to polymerize in situ and to retain the neurotrophins which led to an early beneficial effect on the survival of the iPSC-DAPs. Although the Sprague Dawley rats were cyclosporine immunosuppressed, residual T-cells were found at the transplantation site. These findings suggest that the beneficial effect of the hydrogel might be related to its ability to retain the neurotrophins in the vicinity of the transplant. However, the hydrogel might not show its beneficial effect in the cyclosporine immunosuppressed Sprague Dawley rats because of the residual T-cells population.

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Poster #14. Imaging genetics of brain structure and cognition in murine models of aging and Alzheimer's Disease

David Ashbrook
University of Tennessee Health Science Center

K Hornburg 1, DG Ashbrook 2, J Killmar 2, M McCarty 2, JJ Cook 1, H Mansour 1, Y Tian 1, RW Williams 2, GA Johnson 1

Aging and Alzheimer’s disease both lead to cognitive decline. However, it is unclear how brain structure and connectome changes lead to specific behavioral aspects of this decline, if there are shared underlying molecular mechanisms (e.g. mitochondrial), or if the same structures are targeted. In this project we are using the genetically diverse BXD family and their F1 progeny when crossed to the 5XFAD model (the AD-BXD population), combined with behavioral phenotyping and high-resolution magnetic resonance imaging (MR histology; MRH). A number of brain structures have clear volumetric changes with age and sex in the BXD family. Further, we have identified highly heritable connectome changes due to age, with some strains displaying a clear separation between ‘young’ (107 ± 40 days) and ‘old’ (465 ± 57 days) animals, whereas other strains do not. Similarly, in the AD-BXD population we show a number of behavioral and physical measures which have strong genotype, age and strain effects. We have identified tractography differences between transgenic (Tg) AD-BXD mice and their non-transgenic (Ntg) littermates, with, for example, significant differences between Tg and Ntg in the subiculum of AD-BXD77. Ongoing work is integrating MRH and behavioral phenotypes, to identify potential causal mechanisms. By using this recombinant inbred family, quantitative trait loci can now be mapped for any of these traits, and the data is multiplicatively integrable with the whole phenome of > 13,000 traits. This will allow us to identify gene-by-gene interactions, how these alter brain structure, and ultimately how this leads to behavioral changes.

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Funding Support: NIA R01 AG070913-01, NIA R01 AG075813-01, University of Tennessee Center for Integrative and Translational Genomics, UT-ORNL Governor’s Chair

Poster #15. Impacts of mouse genetics on peripheral neuropathy phenotypes, with or without longevity treatments.

Magdalena Blaszkiewicz
University of Maine

Magdalena Blaszkiewicz, Jake Willows, William David Arnold, Peter Reifsnyder, David Harrison, Kristy L. Townsend

Sex differences underlie the onset and severity of various diseases, and likely interact with genetics in the presentation of phenotypes such as peripheral neuropathy (PN). We previously demonstrated that female mice are protected from diabetic PN, as well as age-related PN until reproductive senescence, but this was not mitigated with rapamycin longevity treatment. 17α- Estradiol (17α-E2) is another validated longevity treatment and is non-feminizing. We used the genetically diverse HET3 mouse to examine the impacts of 17α-E2 on metabolic/adipose functions and peripheral nerve health across aging. The HET3 model leads to reproducible genetic variability in the offspring, making it more relevant to human disease etiology, and allowing measured phenotype data to be statistically compared to an individual animal’s genetics. Middle aged (~51 wks) and older (~84 wks) male HET3 mice received 17α-E2 treatment for 17 weeks. We observed increased grip and contractility torque and improved NMJ function in middle aged 17α-E2 treated mice. However, 17α-E2 treatment improved intraepidermal innervation (a measure of peripheral neuropathy) in older mice only. Reduced fat mass was seen in all 17α-E2 treated mice regardless of age, with improved glucose sensitivity evident only in older male mice. Increased energy expenditure was seen in 17α-E2 treated middle aged mice. Interestingly, these metabolic and neural endpoint data varied by genetic strain. For example, grip strength improvement was evident when C57BL/6 or DBA/2 strain contribution was low. Taken together, 17α-E2 treatment is a translationally relevant way to maintain metabolic and nerve function in aging.

Poster #16. In vitro assessment of biomaterial microcarriers for sustained delivery of dopaminergic neurotrophins in the context of enhancing cell-based brain repair in the Parkinsonian rat brain

Kaushik Narasimhan
University of Galway

Kaushik Narasimhan1, Giulia Comini1, Tommy Patton1, Abrar Hakami2, Benjamin Newland2, Eilis Dowd1

Cell replacement-based therapeutic approaches for Parkinson's disease has long faced hindrance by the poor cell survival post-transplantation, in part due to growth factor deprivation experienced in the adult, diseased brain relative to their pre-implantation levels in the embryonic brain (for primary cell transplants) or in tissue culture (for stem cell-derived transplants). In this context, we investigated the suitability of neurotrophin-loaded polyhedrin microcarriers (co-crystallised with BDNF or GDNF; available as PODS® from Cell Guidance Systems) and PEGDA-SPA cryogel microcarriers (loaded with GDNF or BDNF) as potential biomaterial systems for neurotrophin delivery in a culture. Initial *in vitro* assessment of their morphology was done (using SEM or fluorescent microscopy), followed by their cytocompatibility using AlamarBlue® assay, and neurotrophin loading efficiency (PEGDA-SPA MCs only) and kinetics of neurotrophin release (using ELISA). *In vitro* assessment confirmed the crystalline (PODS®) and spherical (PEGDA-SPA MCs) structures, cytocompatibility with both neurons (SH-SY5Y cells) and microglia (HMC3 cells), as well as their capability for sustained neurotrophin release. These findings offer promising potential of the microcarriers for sustained delivery of neurotrophins to engrafted cells in the context of enhancing cell-based brain repair in PD.

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Funding Support: Science Foundation Ireland

Poster #17. JAX Animal Behavior System (JABS): A machine-vision based phenotyping platform for the laboratory mouse

Vivek Kumar
Jackson Laboratory

Glen Beane, Brian Q. Geuther, Thomas J. Sproule, Anshul Choudhary, Jarek Trapszo, Leinani Hession, Vivek Kohar, **Vivek Kumar***

Automated detection of complex animal behavior remains a challenge in neuroscience. Developments in computer-vision have greatly advanced automated behavior detection and allow high-throughput pre-clinical studies. An integrated hardware and software solution is necessary to facilitate the adoption of these advances in the field of behavioral neurogenetics, particularly for non-computational labs. We have published a series of papers using an open field arena to annotate complex behaviors such as grooming, posture, and gait as well as higher level constructs such as frailty. Here, we present an integrated rodent phenotyping platform, JAX Animal Behavior System (JABS) to the community for data acquisition, machine learning based behavior annotation and classification, classifier sharing, and genetic analysis. JABS Data acquisition module enables uniform data collection with its combination of 3D hardware designs and software for real-time monitoring and video data collection. JABS-Active Learning Module allows behavior annotation, classifier training, and validation. We also present a novel graph-based framework Ethograph that enables efficient boutwise comparison of classifiers. JABS-Database Module allows users to share behavior classifiers and finally the JABS-Analysis Module infers a deposited classifier on a library of 600 open field videos consisting of 60 mouse strains, returns frame level and bout level classifier statistics. In summary, this open-source tool is an ecosystem that allows the neuroscience community to build shared resources for behavior analysis.

The Jackson Laboratory, Bar Harbor, ME.

Poster #18. Phenotyping Individual Differences in Escalation of Fentanyl Self-Administration in Sprague-Dawley Rats.

Michael Bardo
University of Kentucky

PI Ortinski1, R Charnigo2, M Xia1, BA Humburg3, ED Denehy3, JR Turner4 and MT Bardo3

A hallmark criterion of opioid use disorder (OUD) is taking the drug in larger amounts than intended. Phenotyping the escalation of opioid intake may reveal the underlying genetic markers associated with OUD. Male and female Sprague-Dawley rats (n=58) were trained in a sucrose reinforcement task using a progressive ratio schedule; individual differences in responsivity to sucrose were hypothesized to predict escalation of fentanyl intake. Rats were then trained on an FR1 schedule to self-administer fentanyl (2.5 µg/kg/infusion, i.v.) using a 2-lever procedure with a 20-sec signaled time-out (TO). The first 7 sessions were 1 hr and the next 21 sessions were 6 hr. Using latent growth curve modeling, sucrose breakpoints did not predict fentanyl infusions across 1-hr sessions nor escalation of infusions across 6-hr sessions; however, sucrose breakpoints did predict overall infusions earned during 6-hr sessions ($p<0.05$). A mixed effect model showed greater fentanyl intake in females than males during 1-hr sessions ($p<0.01$), but not during 6-hr sessions. Most important, across 6-hr sessions, we used group-based trajectory modeling that probabilistically clustered animals into phenotypes based on the combination of (1) infusions, (2) non-reinforced responses during TO, and (3) inactive lever presses. Four behavioral phenotypes were identified: (1) low escalators (n=17), (2) medium escalators (n=24), (3) high escalators (n=15) and (4) inverted-U escalators (n=2), the latter possibly being aberrations. These results inform ongoing assessment of sequencing-based genomic markers of susceptibility to OUD based on phenotypic expression of escalated opioid intake.

1Department of Neuroscience, 2Departments of Biostatistics and Statistics, 3Department of Psychology, 4Division of Pharmaceutical Sciences, University of Kentucky, Lexington KY, 40536 USA. Funding Support: NIH R01 DA053070 (USA)

Poster #19. Serotonin acutely regulates acoustically-evoked behavior selection in zebrafish through multiple HTR2 receptor subtypes

Roshan Jain
Haverford College

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Neuromodulators such as serotonin (5-HT) regulate many aspects of behavior including mood, social interactions, sleep, and decision-making, to allow animals to flexibly respond to their changing environment. We focus on simple acoustically-evoked behavioral selection in zebrafish to model and understand the impact of serotonin on decision-making and behavioral flexibility. Following sudden acoustic stimuli, zebrafish larvae select between two stereotyped escape behaviors: an explosive short-latency response or a kinematically distinct and weaker long-latency response, biasing their selection based on the perceived threat of the stimuli, environmental context, and recent stimulus history. Through an array of pharmacological antagonists and agonists of various serotonin receptors, we have identified distinct serotonin receptor subsets that acutely bias which escape behaviors zebrafish select in response to acoustic stimuli. To pinpoint the specific serotonin receptors responsible for biasing this behavior selection, we designed

CRISPR/Cas9 gene knockout tools to target candidate serotonin receptor subtype genes. Through combined pharmacology and genetics we demonstrate that 5-HT_{2B} and 5-HT_{2CL2} receptor activity promotes the selection of long-latency escape behaviors over short-latency responses. Surprisingly we also find that the related paralogous 5-HT_{2CL1} receptor biases behavior selection in the opposite direction, promoting short-latency escape behavior. Together this work reveals multiple receptor mechanisms through which serotonin bi-directionally modulates simple and ethologically relevant vertebrate decision-making following acoustic threat.

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Poster #20. Synergistic, long-term effects of glutamate dehydrogenase 1 deficiency and mild stress on cognitive function and mPFC gene and miRNA expression

Kfir Asraf

Haifa University

Kfir Asraf12, Hiba Zaidan12 and Inna Gaisler-Salomon12

In order to investigate gene x environment interactions in a mouse model of cognitive deficits, we examined the impact of mild stress in mice genetically modified to express deficient levels of glutamate dehydrogenase 1 (GDH). GDH (gene name: *Glud1*) plays a central role in glutamate metabolism and is downregulated in the hippocampus of patients with schizophrenia. Mice with a full deletion of *Glud1* in CNS (C-*Glud1-/-* mice) previously showed abnormally high glutamate levels and a wide range of behavioral deficits. Here, we exposed heterozygous C-*Glud1*+/- mice and their C-Cre+ controls to mild stress in early adulthood. Stress-naïve mice of both genotypes were used as controls. Seven days later, mice were tested in a battery of behavioral tests assessing locomotor activity, social behavior and cognitive function. Fourteen days following behavior, medial prefrontal cortex samples were removed and analyzed for expression changes in transcriptome and select microRNA molecules using RNA-seq and RT-PCR, respectively. In a second cohort, brains were extracted immediately after the stress. Stress-exposed C-*Glud1*+/- mice showed novelty-induced hypo-locomotion and impaired spatial acquisition and reversal. Transcriptomic analyses revealed vast changes in glutamatergic, GABAergic and stress-related genes, which were unique to stress-exposed *Glud1*-deficient mice. These behavioral and molecular deficits were absent in stress-naïve CNS-*Glud1*+/- mice and in stress-exposed CNS-Cre+ controls. MiR203-5p emerged as a potential mechanism for the effect of stress exposure. *Conclusions:* Our findings indicate that CNS-*Glud1*+/- mice exposed to stress in early adulthood display cognitive deficits, as well as molecular abnormalities, which are also relevant to stress exposure and psychopathology.

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Poster #21. The impact of complement-based polygenic risk score for schizophrenia on cognitive performance via cortical thickness in schizophrenia and healthy adults

Dijana Ostojic

University of Galway

D Ostojic 1, E Corley 2, G Donohoe 3

Schizophrenia is a severe psychiatric disorder. Cognitive impairments have been defined as core symptoms of schizophrenia. Recent studies have demonstrated that variation in complement genes as a whole is a better predictor of cognitive performance than variation in individual complement genes alone. This study investigated whether the association between complement genes and different cognitive impairments observed in schizophrenia is mediated via whole-brain cortical thickness. A moderated mediation analysis was employed to investigate the mediation effect of cortical thickness and the moderation effect of diagnosis on the relationship between complement-based schizophrenia polygenic risk score and cognitive impairments. A direct effect of complement-based schizophrenia polygenic risk score on verbal (b = .50, p = .045, 95% CI [.01, .99]) and non-verbal (b = -3.04, p = .049, 95% CI [-6.05, -.01]) working memory performance for patients was observed. These relationships did not survive multiple testing correction. The conditional process analyses revealed no mediation or moderated mediation effects. Only diagnosis was observed to moderate the relationship between complement-based schizophrenia polygenic risk score and verbal working memory performance (b = .58, p = .025, 95% CI [.08, 1.09]). We concluded that the relationship between high complement polygenic risk score and poor cognitive performance was not mediated by whole-brain cortical thickness. However, due to a number of methodological issues such as small sample size and unequal group size, one should interpret these findings cautiously.

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Poster #22. The Role Of Active Zone Proteins And Their Interactions In Alcohol Sensitivity In Drosophila

Gregg Roman

University of Mississippi

Gaurav Shrestha1, Gregg Roman2

Unc13 is a presynaptic active zone protein involved in synaptic vesicle docking. Alcohol binds to the C1 domain of Unc13, inhibiting DAG binding and reducing Unc13 activity. The Drosophila Unc13 gene has 2 major variants, Dunc13A and Dunc13B, which differ in their N-terminal domains. Dunc13A will bind RIM and is located close to BRP in the active zone, while Dunc13B binds liprin and is located farther from BRP. *Dunc-13*^{P84200}/+ heterozygotes lack one functional copy of both the Dunc13A and Dunc13B isoforms and are resistant to alcohol sedation sensitivity and presynaptic inhibition by alcohol, and show increased alcohol self-administration. Herein, we examine the individual contributions of these two isoforms to alcohol behavioral sensitivity. Surprisingly, we found that heterozygotes for a *Dunc13A* Null mutant were more sensitive to alcohol sedation than wildtype controls however, heterozygotes for the *Dunc13B* Null mutation's phenotype were not significantly different from the control. To determine if RIM also regulates alcohol sensitivity, we examined the sedation sensitivity phenotype of the *RIM*^{MB07541} insertional mutant and the *RIM*^{EX73} null mutant. Both *RIM* mutants displayed dominant increases in alcohol sensitivity, similar to that found in *Dunc13A* mutants. Interestingly, the *RIM*^{MB07541}/+; *Dunc-13*^{P84200}/+ double heterozygotes were not significantly different from wild-type controls, indicating a genetic interaction between these mutations in regulating alcohol sedation sensitivity. Our data indicate that the Dunc13 isoforms have distinct and interacting roles in regulating ethanol sensitivity, which may include changes in the gene expression of specific active zone proteins regulated by *Dunc13* activity.

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Virtual Poster. TrkB.T1 receptor in the mechanisms of genetically-determined depressivelike behavior in mice

Marah Alsalloum
Novosibirsk State University

https://ibangs.memberclicks.net/assets/documents/Poster_Marah%20Alsalloum.pdf

Alsalloum M.*#, Ilchibaeva T.* Tsybko A.*, Eremin D.*, Naumenko V.*

Depression is a mental disorder that significantly reduces quality of life, and the discovery
of new drug targets is still an urgent problem for modern neuroscience. BDNF and its receptors were found to be involved in the mechanisms of depression and antidepressants action. In this study we focused on the less-studied truncated isoform of TrkB receptor: TrkB.T1 receptor. We have found that the TrkB.T1 receptor level is reduced in the hippocampus of characterized by genetically-determined depressive-like behavior ASC mice (Antidepressant Sensitive Cataleptics) compared to “normal” C57BL/6 mice. Next, overexpression of TrkB.T1 receptor in hippocampal neurons was induced to clarify the role of TrkB.T1 receptor in the mechanisms of depressive-like behavior. TrkB.T1 receptor overexpression decreased BDNF protein level in the hippocampus. On behavioral level, TrkB.T1 receptor overexpression decreased locomotor activity, slightly increased anxiety and depressive-like behavior, decreased exploration activity, while did not affect learning and memory. Most significantly, TrkB.T1 receptor overexpression decreased aggression and enhanced social behavior in the mice from experimental group. Our work showed that TrkB.T1 receptor involved in the regulation of aggression, social behavior, anxiety, and depressive-like behavior in ASC mice. Considering our findings, we believe, that hippocampal TrkB.T1 receptor might serve as a drug target for behavioral pathologies
correction.

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Poster #24. Social space: what can we learn from a fly?

Anne Simon
Western University

Yost RT[1], Robinson JW[1], Bechard AT[1], Alaka W[1], Simon AF[1]

Before engaging in complex social interactions, flies must determine their preferred social space. Indeed, all motile organisms, from bacteria to humans, including *D. melanogaster*, display a preferred inter-individual (or social) distance that can be affected by genetics, experience and/or the environment.

One of the goals of my lab, is to better understand the neurogenetic underpinnings of social space determination. We have shown that social spacing in *D. melanogaster* can be influenced by a variety of intrinsic and extrinsic factors, such as mating status, social enrichment, genes, and environmental conditions, and an interplay between those. A sex specific neural circuit is emerging as a modulator of social spacing: it involves dopaminergic signalling, and two major brain structures: the mushroom bodies, and the protocerebral bridge.

In addition, the neural bases of social spacing are starting to be elucidated. And several of the players – from neurotransmitters to post-synaptic proteins – are conserved through evolution. At the synaptic level, we have shown that Neurobeachin (an anchor protein) and Neuroligin (a cell adhesion protein) are implicated in social space, as well. Both of those postsynaptic proteins have human homologues that are candidate genes for Autism Spectrum Disorders (ASDs). We performed genetic screens to identify other players in this response to others. I will present the recent progress my research team has made in elucidating the basis underlying the decision-making process to come to around 2-body length away from another fly.

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Funding Support: This project was funded by Western University internal scholarships to WA, and in addition Ontario provincial grants to RTY, JWR and ATB; NSERC Fellowship to RTY and JWR; NSERC Discovery grants 04275-2015 and 05054-2022 to AFS.

Poster #25. Enhancing anandamide signaling restores depression-like phenotype and sex-dependent alterations in micro-RNAs in rats exposed to early life stress

Anya Portugalov
University of Haifa

Anna Portugalov 1,2, Hiba Zaidan 1,2, Inna Gaisler-Salomon 1,2 and Irit Akirav 1,2

Early life stress (ELS) significantly increases predisposition to psychopathologies, including depression. Here, we compared the effects of treatment with the fatty acid amide hydrolase (FAAH) inhibitor, URB597 that increases anandamide levels and the selective serotonin reuptake inhibitor (SSRI), paroxetine, on depressive-like behavior and the expression of microRNAs (miRs) associated with depression and the serotonergic system in the medial prefrontal cortex (mPFC) of rats exposed to ELS. Male and female rats were exposed to ELS using the "Limited Bedding and Nesting" paradigm, in which dams had limited access to nesting material, from postnatal day (P)7 to P14. During P45 to P60 (late adolescence) URB597 (0.4 mg/kg) or paroxetine (5mg/kg), were administered i.p. for 2 weeks. On P90 (adulthood) rats were tested for depressive-like behavior and the expression of miR-16 and miR-135a. Adult male and female rats demonstrated depressive-like behavior, such as decreased social behavior and increased learned helplessness. Chronic treatment during post-adolescence with URB597, but not paroxetine, reversed these behaviors. In the mPFC, ELS males demonstrated a decrease in miR-16 and ELS females demonstrated a decrease in miR-135a. Importantly, URB597, that reversed depressive-like behavior in both sexes, also normalized mPFC miR-16 and miR-135a expression abnormalities in males and females, respectively. Our findings show for the first time that enhancing anandamide signaling can prevent ELS-induced decrease in mPFC miRs and associated depression-like phenotype in both sexes. This may advance our knowledge of pathways dysfunctional in depression in cortical areas and suggest a mechanism for the beneficial effects of enhancing endocannabinoid signaling.

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Poster #26. The Arnt2-dependent prefrontal somatostatin interneurons control affective empathy in mice

Sehoon Keum
Center for Cognition and Sociality, Institute for Basic Science

Jiye Choi1, Arie Kim1, Eunsoo Yoo1, Sungjoon Choi1, Jiyeon Kim1, Yoochul Jang1, Sehyun Chae2*, Sehoon Keum1*

The empathic ability to understand the emotional states of others is crucial for human social interactions, and its abnormalities manifest in various psychiatric disorders. While there is a considerable genetic contribution to individual variability in human empathy, very little is known about the specific genes that regulate empathic responses. Observational fear is a useful behavioral paradigm measuring affective empathy in rodents. In observational fear, vicarious freezing is highly variable and strain dependent, indicating that the innate response in empathic fear is under strong genetic control. Here, we exploited robust inbred mouse strain differences and uncovered a quantitative trait locus (QTL) associated with observational fear. The genetically isolated QTL locus in congenic mice refined the critical

interval that determines the level of vicarious freezing. Through the analysis of RNAseq transcriptomes in the anterior cingulate cortex (ACC) of QTL-linked genes, we have identified Arnt2 (Aryl hydrocarbon receptor nuclear translocator 2) as a causative gene. Using a virus-based approach to directly regulate Arnt2 function, we demonstrated that downregulating Arnt2 expression in the ACC altered observational fear. Furthermore, selective deletion of Arnt2 in somatostatinexpressing (SST) inhibitory neurons significantly reduced observational fear and altered calcium dynamics of SST interneurons in the ACC during observational fear task. These findings highlight the essential role of Arnt2 in observational fear through its functional actions in the cortical microcircuit and provide new insights into the neurobiological mechanisms underlying affective empathy.

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Poster #27. Alcohol-induced sleep dysregulation in Drosophila is dependent on the neuropeptide PDF

Alfredo Ghezzi
University of Puerto Rico

ME Ramirez-Roman[1], NL Fuenzalida-Uribe[1], G Ayala-Santiago[1], JL Agosto[1], A Ghezzi[1*]

Alcohol exposure 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 neuronal and genetic pathways that control the effects of alcohol on sleep are currently unknown, thus, limiting our efforts to find effective treatment. In this study, we conduct a mechanistic exploration of the relationships between alcohol and sleep alterations using a Drosophila model system. We show that the genetic manipulation of the ventral lateral neurons (LNv) —a set of neurons known to control sleep in Drosophila— disrupts alcohol sensitivity and tolerance. Moreover, we show that alcohol exposure induces a series of alterations in sleep patterns that last for several days. Our results demonstrate that a single alcohol exposure promotes daytime sleep, alters sleep structure during the night, and reduces morning anticipatory behavior. In addition, we show that some of these alterations are partially dependent on the activity of the neuropeptide PDF, a key element in the regulation of sleep architecture. We propose that alcohol-induced sleep disruption stems from alterations in the activity of the PDF-releasing LNv neurons and that these alterations are similar to those that produce alcohol tolerance.

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Poster #28. Repeated Daily Binge Alcohol Drinking Leads to Sex-specific Alterations in Corticostriatal Theta Coherence, Home Cage Locomotion, and Endogenous Circadian Rhythms

David Linsenbardt
University of New Mexico

D. Linsenbardt[1], C. Ardinger[2], M. Orozco[1], T. Huffman[1] M. Westenskow[1]

Given the high propensity of binge alcohol drinking (BD) and the profound deleterious consequences it is associated with, there is a need to identify the neurobiological and neurobehavioral mechanisms that regulate, and are regulated by, repeated BD experiences. We provided mice with daily access to water or alcohol for 14 consecutive days using drinking-in-the-dark (DID) procedures. In one cohort we monitored extracellular electrophysiological activity simultaneously in the medial prefrontal cortex (mPFC) and nucleus accumbens (Nac) during DID sessions. In another cohort we monitored home cage locomotion 24/7 using IR cameras. The first BD experience led to significant decreases in corticostriatal theta coherence in both sexes that decreased further following 2 weeks of daily BD in females only; males displayed tolerance to BD-induced decreases in corticostriatal theta coherence whereas females displayed a sensitized response. BD was also associated with increases in 24hr home cage locomotion in females that emerged only following DID sessions, and decreases in 24hr home cage locomotion in males indicative of BD-induced sedation. Finally, free-running conditions had no impact on circadian periodicity in BD male subjects only; all other subjects displayed the expected shifts in periodicity. These data indicate that repeated BD leads to functional corticostriatal decoupling in females potentially as a consequence of daily acute withdrawal-associated neurobehavioral hyperexcitability. These data further indicate that repeated BD in males is associated with entrained corticostriatal coupling that may serve to stabilize endogenous circadian rhythms potentially as a consequence BD-induced neurobehavioral depression.

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Poster #23. Circuits and molecules that govern habituation to repeated footshocks in Drosophila

Efthimios Skoulakis
Institute for Fundamental Biomedical Research

Efthimios MC Skoulakis, Eleni Aplakidou, Alexandros Charonitakis, Kyriaki Foka, Eirini-Maria Georganta, Ilianna Roussou and Ourania Semelidou.

Habituation is a conserved adaptive process essential for incoming information assessment, which drives behavioral response decrement to recurrent inconsequential stimuli and does not involve sensory adaptation, or fatigue. We have established a number of habituation protocols to persistent odor stimulation and recurrent mild electric footshocks for Drosophila. Herein we report on the role of distinct mushroom body neurons to the latency to habituate and habituation to recurrent footshocks. To understand the molecular mechanisms that govern the transitions among the distinct habituation phases, we have performed genetic screens for mutants presenting shortened or prolonged habituation latency and we report on molecular pathways engaged within mushroom body neurons and are essential for progression through the proposed phases of habituation to footshocks.

Institute for Fundamental Biomedical Research. Biomedical Sciences Research Center “Alexander Fleming” Vari, 16672 Greece

Symposium 3: Impact of Environmental Exposures Across Species and Lifespan: Untangling complex regulation of genes and behavior

Time: Wednesday, 24/May/2023: 9:00am · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Kristin Hamre
Session Chair: Megan Mulligan

Impact of Environmental Exposures Across Species and Lifespan: Untangling complex regulation of genes and behavior

Kristin Hamre
Univ. of Tennessee Health Science Center

Symposium Chairs: Kristin Hamre and Megan Mulligan

Symposium Abstract:

All four talks involve the study of complex traits and how they are influenced by various factors such as cis-regulatory variation, parent-of-origin effects, environmental conditions, and gene-by-environment interactions. Each speaker utilizes different species (chick, rat, and mouse) to study the effects of various exposures, such as diet, rearing environment, heat stress and prenatal alcohol and cannabis exposure, on gene expression and/or brain and behavioral development. Finally, all four talks highlight the importance of incorporating or controlling for environmental variables to accurately understand the effects of a particular context or exposure on complex trait variation.

Multi-pronged molecular approach to identify regulatory mechanisms mediating the impact of prenatal alcohol exposure on the developing hindbrain

Daniel Goldowitz
University of British Columbia

N. Elazzabi1, KM Hamre2, Dan Goldowitz1

The identification of genetic factors that underlie vulnerability for FASD is still at an early stage of discovery. Mice have proven to be an excellent organism to study this issue. In particular, C57BL/6 mice are extremely sensitive to the effects of ethanol while others DBA/2J are quite resistant, and a genetic basis for this difference has been shown. Here, we utilized a prenatal alcohol exposure (PAE) mouse model to collect E9.5 hindbrains generated from reciprocal F1 hybrids using the inbred strains C57BL/6 and DBA/2J. 3-4 replicates of ethanol exposed and maltose dextran control hindbrains were collected. We used a newly developed pipeline for methylomic and epigenomic analysis (MEA) [1] for a multi-pronged approach (allele-specific and allelic agnostic RNA-seq analysis). Genes with $\log_2$ fold changes in expression >0.5 and <0.5 with adjusted p value less than 0.1 were considered differentially expressed in this analysis.We find: (1) genes that demonstrate gene x environment (GxE) interactions providing molecular insights into the phenotype of enhanced cell death in the hindbrain seen in the susceptible strain; (2) *cis*-acting factors mediating GxE interactions; (3) a strong C57BL/6 maternal effect on increasing susceptibility to ethanol exposure; and (4) that certain imprinted alleles, involved in fetal growth, are more sensitive to ethanol-induced expression changes than other alleles. These findings provide a fertile ground for understanding the genes and environment that underlie PAE in the mouse.

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Choline as a treatment for prenatal drug exposure

Jennifer Thomas
San Diego University

JD Thomas, JA Baker, KJ Thomas, CR Rodriguez

Prenatal alcohol exposure can alter behavioral development, leading to a range of outcomes referred to as fetal alcohol spectrum disorders. Using an animal model, we have found that early treatment with the essential nutrient choline can improve brain and behavioral development in subjects exposed to alcohol prenatally, a finding now being translated to clinical trials. Specifically, we have found that choline administered during the prenatal period can improve a wide range of behavioral outcomes, whereas choline administered postnatally improves behaviors that depend on the functional integrity of the hippocampus and/or prefrontal cortex. Thus, choline can improve hippocampal function even when administered after the alcohol insult. Our data indicate that choline alters hippocampal development through several mechanisms, including altered cholinergic functioning, epigenetic changes, and long-lasting modifications of neuroinflammation. But not only can choline improve outcome following prenatal alcohol, we now have preliminary data indicating that early choline may also reduce the severity of cognitive deficits associated with prenatal cannabis exposure. Specifically, early postnatal choline may enhance spatial memory on the Morris maze in subjects exposed to prenatal tetrahydrocannabinol, the most psychoactive component in cannabis. These data illustrate how early nutritional factors can alter developmental trajectory following prenatal drug exposure, findings with important implications for treatment of individuals exposed to drugs prenatally.

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Funding Support: NIAAA R37 AA012446

Sex and diet modulate allele-specific gene regulation

Celine St. Pierre
Washington University in St. Louis

CL St. Pierre1, T Wang1,2, HA Lawson1

Allele-specific effects have widespread impacts on gene regulation and complex traits. Genetic and epigenetic factors cause allele-specific biases in gene expression and methylation patterns. Depending on a gene's function, these allelic imbalances can have phenotypic consequences in complex traits. However, how environmental factors contribute to allele-specific gene regulation remains understudied. Here, we explored how external (diet) and internal (sex) environmental signals influence allele-specific expression (ASE) and methylation (ASM) patterns. Male and female mice from a F_1 reciprocal cross of the LG/J and SM/J inbred mouse strains were fed a high-fat or low-fat diet. We generated RNAseq transcriptomes and whole-genome bisulfite-converted methylomes from three metabolic tissues: hypothalamus, white adipose, and liver. We harnessed strain-specific genetic variants to distinguish between two allele-specific classes: parent-of-origin dependent (allelic imbalance based on parental origin) and sequence dependent (allelic

imbalance based on genetic background). We found that both classes of ASE and ASM patterns are highly dependent on tissue type and environmental factors. They vary across metabolic tissues, between males and females, and in response to dietary environments. We also found several cases where a gene's expression bias can be explained by a nearby methylation bias. Finally, we integrated these results with QTL data from published advanced intercrosses of the LG/J and SM/J strains. Our ASE genes are often enriched in QTLs for metabolic traits in an environment-dependent manner, highlighting how this orthogonal approach can prioritize candidate genes for functional validation. Together, our results provide a systems biology perspective on the gene-by-environment architecture underlying complex traits.

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Funding Support: NSF GRFP (DGE2139839), Washington University Department of Genetics (USA), NIDDK K01 DK095003, NIEHS U24 ES026699, NIDDK P30 DK020579

Epigenetic regulation of embryonic and early life heat stress on life-long and heritable responses in chicks

Noam Meiri
The Volcani Center

Noam Meiri[1], Asaf Marco[2], Tomer Cramer [1,2], Tali Rosenberg [1,2], Tatiana Kisliouk [1]

Stressful events during the embryonic or early life periods might lead to stress resilience or vulnerability throughout life and might be transmitted to the next generation.

Here we demonstrate that heat stress during the critical developmental period of thermal-control establishment, affects both body temperature and the expression of CRH in the hypothalamic paraventricular nucleus, later in life. Both CRH and body temperature were 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 vice versa in vulnerable ones.

In a second effort, we addressed the question of whether behavioral traits are heritable. A major obstacle in demonstrating transgenerational inheritance in mammals originates from the maternal environment's effect on offspring phenotype. To overcome this challenge, we used in ovo embryonic heat conditioning of first-generation chicks and assessed the effect on their untreated offspring. We demonstrate heredity of both heat and immunological resilience, confirmed by a reduced fibril response in untreated offspring to either heat or LPS challenge. Furthermore, we demonstrate association between epigenetic mechanisms and trait heritability, by genome-wide DNA-methylation analysis in the anterior preoptic hypothalamus of untreated offspring. Finally, we demonstrate a possible role for chromatin architecture in epigenetic heritability.

Conclusively, we suggest a multilevel epigenetic regulation for stress responses and trait heredity.

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Funding Support: United States-Israel Binational Science Foundation (BSF) (Grant No. 2020663); United States National Science Foundation (NSF) (No. 2041923); Israel Science Foundation (grant no. 2587/21).

Selected Talks 2

Time: Wednesday, 24/May/2023: 11:30am · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Sam Gottlieb
Session Chair: Kristin Scaplen

Role of vascular cell types in the neuroimmune mouse model of escalated ethanol consumption: Single nucleus RNA-Seq study

Brent Kisby
Texas Tech University Health Sciences Center

Brent R. Kisby, Michelle McManus, Sambantham Shanmuganum, Igor Ponomarev

Escalation of alcohol (ethanol) consumption is one of eleven criteria for alcohol use disorder (AUD). Innate immune activation by repeated injections of the TLR3 agonist, Poly(I:C) (PIC), increases alcohol consumption in C57BL/6J (B6) male mice. To investigate the underlying mechanisms of this effect, we used single nucleus RNA-Seq (snRNA-Seq) to identify brain cell types affected by innate immune activation. B6 male mice were given 9 injections of either saline or 10 mg/kg of PIC every 4 days while given access to Every-Other-Day two bottle choice 15% ethanol, resulting in increased alcohol consumption in the PIC group. Twenty-four hours after the final alcohol session, brains were harvested, flash-frozen and subjected to snRNA-Seq analysis. We identified 40 discrete graph-based clusters (49,763 nuclei) corresponding to specific cell types and determined genes differentially expressed (DEGs) between saline and PIC groups within each cell type. Cell types most affected my PIC included endothelial cells (ECs), smooth muscle cells (SMCs), pericytes, and perivascular fibroblasts (PVF), suggesting that vascular cell types play an important role in the neuroimmune signaling. Examples of cell type - specific DEGs include *Cldn5* for ECs, *Slc7a5* for SMCs, and *Slc38a2* for PVF – genes important for cellular functions. These findings are consistent with our preliminary bulk sequencing data showing significant effects of innate immune activation on ECs. Taken together, the data suggest that vascular cell types may contribute to the immune-modulated transition from low to elevated levels of ethanol consumption. These data also provide rationale for development of vasculature-based therapeutics for AUD.

Texas Tech University Health Sciences Center; Department of Pharmacology and Neuroscience, Lubbock, TX

Prolonged partner separation erodes nucleus accumbens transcriptional signatures of pair bonding in male prairie voles

Julie Sadino
University of Colorado Boulder

JM Sadino1, XG Bradeen2, 3, CJ Kelly1, 4, LE Brusman1, DM Walker5, ZR Donaldson1, 2

Spousal loss is emotionally painful and traumatic. However, for most people, the severity of grief and its maladaptive effects subside over time via an understudied adaptive process. Here, we used socially monogamous prairie voles (*Microtus ochrogaster*), which form pair bonds akin to human spousal relationships, to assess the neurobiological underpinnings of bonding and loss adaptation. We test the hypothesis that extended partner separation causes pair bond transcriptional signatures within the Nucleus Accumbens (NAc) to erode. Pairs were cohoused for 2 weeks and then either remained paired or were separated for 48 hours or 4 weeks before collecting fresh NAc tissue for RNAseq. Opposite-sex pair bonding led to changes in accumbal transcription that were stably maintained while animals remained paired but eroded following prolonged partner separation. Eroded pair bond genes are associated with gliogenesis and myelination, suggesting a previously undescribed role for glia in pair bonding and loss. We are validating these RNAseq predictions by investigating glial-related plasticity via lineage mapping and immunolabeling in voles experiencing bonding or loss. This work advances our understanding of the processes that allow individuals to overcome grief and perhaps enable the formation of a subsequent bond with a new partner.

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Validating Zhx2 in oxycodone metabolite (oxymorphone) brain concentration and behavior via reciprocal gene editing and viral manipulation of gene expression in BALB/c substrains

William Lynch
Boston University

William B. Lynch1,2,3, Ida Kazerani1,4, Gabriel A. Saavedra1,5, Ava Farnan1, Binh-Minh Nguyen1, Jacob A. Beierle 1,3,6, Camron D. Bryant1,2,3

Opioid Use Disorder (OUD) maintains epidemic proportions in the U.S., with current pharmacological treatments limited to opioid substitution therapy. Sensitivity to the subjective and physiological responses to opioids has a genetic component that could influence addiction liability. We identified Zhx2 as a candidate gene underlying increased oxycodone (OXY) metabolite brain concentration in BALB/cJ (J) vs. BALB/cByJ (By) females. The metabolite, oxymorphone (OMOR), is more potent and efficacious and could enhance state-dependent learning and recall of OXY-induced conditioned place preference (CPP) in J vs. By females. A structural intronic variant causes a significant reduction in Zhx2 expression in J vs. By mice. Thus, here, we tested the role of this variant in OMOR levels and OXY behaviors through gene editing of the variant, through modeling Zhx2 loss-of-function via exon 3 deletion, and through virally manipulating Zhx2. We are still validating the Zhx2 variant on OMOR and behavior. Following AAV-mediated liver overexpression of Zhx2, J females showed an increase in state-dependent OXY reward learning and a decrease in OXY-induced locomotor sensitivity. We also observed an increase in Cyp2d22 RNA, thus providing a potential intermediary mechanism linking Zhx2 with differential brain OMOR concentration. Complementary to these results, there was an increase in OXY-induced locomotor sensitivity when Zhx2 was knocked out and an increase in state-dependent reward learning. Our work supports validation of Zhx2 as a quantitative trait gene underlying brain OMOR concentration and behavior, which could increase our understanding of OXY addiction liability in humans.

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Phenotypic Correlates of Initial Subjective Rewarding Effects of Alcohol

Judy Grisel
Bucknell University

Holly E. Jones1, Emma L. Keller1, Leona H. Gagnon2, Ashley Olson2, Troy D. Wilcox2, Elissa J. Chesler2, Judith E. Grisel1

Subjective experiences from addictive drugs vary substantially between individuals and predict a liability for substance use disorders. Understanding the heritable risk for alcohol use disorders (AUDs) has been hampered by a lack of animal models that isolate and assess initial subjective rewarding properties of the drug. This study utilized a single-exposure conditioned place preference (SE-CPP) paradigm to identify phenotypic and genetic correlates of initial subjective rewarding effects of alcohol (EtOH) in diversity outbred (DO) mice. We assessed the relationship between SE-CPP and basal anxiety using a marble burying task and conventional light dark assay. One-hundred male and female diversity outbred mice were tested in a Marble Burying task at 7-8 weeks, followed by the Light-Dark Box assay at 9-10 weeks. At 11-12 weeks they were assessed for SE-CPP: animals received one of two IP injections (1.5 g/kg EtOH and equivolume saline) on either Day1 or Day3 in two distinct contexts (counterbalanced) and were tested for their context preference on Day5. Overall, SE-CPP was evident, as mice preferred the context associated with a single injection of EtOH over one associated with saline, with substantial genetic variation. In females, but not males, SE-CPP was predicted by the number of marbles buried 4 weeks earlier. There were no correlations among variables in males. Genotyping will be used to estimate heritability of SE-CPP, and quantify the extent of genetic variation associated with this multidimensional phenotype. This research contributes to better understanding the influence of sex and genetic variation in the risk for AUDs.

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What role do context specific enhancers play in brain function, behaviour and disease?

Alasdair MacKenzie
University of Aberdeen

Alasdair MacKenzie1, Andrew McEwan1, Andrew McIntosh2, Chris Murgatroyd3, Greg Hutchings1.

Genome wide association studies have suggested that most disease associated SNPs (>90%) occur outside of the 1.7% of the human genome that makes proteins. So, what information is contained within the non-coding region of the human genome which is so important for human health? It is no surprise that, in addition to producing correct proteins, genes also need to be turned on in the correct cells, at the correct times and in the correct amounts to produce a healthy brain. Much of this job is handled by enigmatic gene regulatory elements called enhancers. The work of our lab focuses on the identification and in-vivo characterisation of polymorphic and context specific enhancer regions which have been conserved in all higher vertebrates. We have identified conserved enhancers that control the tissue specific expression of genes including the cannabinoid-1 receptor (CB1), galanin (GAL) and BDNF in hypothalamus, amygdala and hippocampus. We have used a combination of CRISPR genome editing and behavioural analysis in mice to define the mechanisms of action of these enhancers and their roles in modulating behaviours such as anxiety, ethanol intake fat consumption and drug response. Further experiments have also defined the effects of polymorphic variation and epigenetic modification on their activity. Critically, analysis of allelic variants in the UK Biobank cohort has further supported the role of these enhancers in changes in human physiology associated with disease. By understanding how enhancers work, and how they are affected by SNPs and DNA-methylation, we hope to better understand susceptibility to disorders such as addiction, anxiety and obesity within the human population and aid in the development of personalised therapeutics.

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Funding support: BBSRC project grants (BB/N017544/1 and BB/W017598/1), Medical Research Scotland (PhD-50366-2021 and PhD-719-2013) and Wellcome Trust Strategic Award (Reference 104036/Z/14/Z).

Symposium 4: Investigating convergent biological mechanisms across neuropsychiatric disorders

Time: Wednesday, 24/May/2023: 2:00pm · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Chang-Hui Pak

Investigating convergent biological mechanisms across neuropsychiatric disorders

ChangHui Pak
University of Massachusetts Amherst

Symposium Chair: ChangHui Pak

Symposium Abstract:
Recent advances in genetic discoveries and technology developments have led to the identification of high-confidence common and rare genetic variants, gene-network based discoveries from postmortem tissues at bulk and single-cell levels, and novel disease insights from human induced pluripotent stem cells. What is clearly emerging from these studies is that there are points of biological convergence across complex brain disorders, which indicate shared disease etiology and critical vulnerabilities at the molecular and cellular levels. In this symposium, we will highlight novel discoveries in the efforts to understand the underlying biological mechanisms across neuropsychiatric disorders, as well as the ongoing efforts in the iPSC-based neural systems to better recapitulate neurodevelopment and identify disease-specific mechanisms. Talks included are from diverse investigators stemming from multiple countries, who utilize multidisciplinary approaches in human genetics, functional genomics, and neuroscience. The group consists of two women and two men across different institutions and ranks. The talks will reveal novel insight on the genetic basis of psychiatric disorders using human multi-omic data, human iPSC cell models, and mouse models. This breadth of models provides a mechanistic genes-brains-behavior approach to understanding psychiatric disease.

Large-scale functional genomic profiling in the developing human brain implicates isoform dysregulation in psychiatric disorder etiopathogenesis

Michael Gandal
University of Pennsylvania

Cindy Wen[1-2], Michael Margolis[1-2], Rujia Dai[3], PsychENCODE Consortium, Chunyu Liu[3], Michael J. Gandal[1-2;4-5]

Genomic regulatory elements active in the developing human brain are notably enriched in genetic risk for neuropsychiatric disorders, including autism spectrum disorder (ASD), schizophrenia, and bipolar disorder. However, prioritizing the specific risk genes and candidate molecular mechanisms underlying these genetic enrichments has been hindered by the lack of a single unified large-scale gene regulatory atlas of human brain development. Here, we uniformly process and systematically characterize gene, isoform, and splicing quantitative trait loci (xQTLs) in 672 fetal brain samples from unique subjects across multiple ancestral populations. We identify 15,752 genes harboring a significant xQTL and map 3,739 eQTLs to a specific cellular context. We observe a striking drop in gene expression and splicing heritability as the human brain develops. Isoform-level regulation, particularly in the second trimester, mediates the greatest proportion of heritability across multiple psychiatric GWAS, compared with eQTLs. Via colocalization and TWAS, we prioritize biological mechanisms for ~60% of GWAS loci across five neuropsychiatric disorders, nearly two-fold that observed in the adult brain, identifying dozens of new risk mechanisms and convergence with rare variant implicated genes. Finally, we build a comprehensive set of developmentally regulated gene and isoform co-expression networks capturing unique cell-type-specific patterns of genetic enrichment across disorders. Together, this work provides a comprehensive view of genetic regulation across human brain development as well as the stage- and cell type-informed mechanistic underpinnings of neuropsychiatric disorders.

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Synaptic dysfunction as the driving mechanism across neuropsychiatric disorders: recent findings from human iPSC-derived induced neurons and brain organoids

ChangHui Pak
University of Massachusetts Amherst

ChangHui Pak[1]

[1]Department of Biochemistry and Molecular Biology, UMass Amherst, Amherst, MA 01003 USA

Recent advances in genetic discoveries and technology developments have accelerated the identification of high-confidence common and rare genetic variants, gene-network based discoveries from postmortem tissues at bulk and single-cell levels, and novel disease insights from human induced pluripotent stem cells (iPSCs). What is clearly emerging from these studies is that there are points of biological convergence across complex brain disorders, which indicate shared disease etiology and critical vulnerabilities at the molecular and cellular levels. Despite differences in the developmental origin of the disease, ultimately, the impact of these vulnerabilities on synaptic development, maturation and function could be a key driving mechanism for disease etiology and risk. In this talk, I will highlight the latest findings from patient iPSC-derived brain organoids and induced neuronal cells to understand the underlying biological mechanisms in schizophrenia and autism spectrum disorders. I will also touch upon ongoing efforts in improving iPSC-based neural systems to better recapitulate neurodevelopment and study disease-specific mechanisms.

Alleviating SYNGAP1 haploinsufficiency in disease models by redirecting alternative splicing

Xiaochang Zhang
University of Chicago

The Ras GTPase-activating protein SYNGAP1 plays a central role in synaptic plasticity, and de novo SYNGAP1 mutations are among the most frequent causes of autism and intellectual disability. How SYNGAP1 is regulated during development and how to treat SYNGAP1-associated haploinsufficiency remain challenging questions. We characterize an alternative 3' splice site (A3SS) of SYNGAP1 that induces nonsense-mediated mRNA decay (A3SS-NMD) in mouse and human neural development. PTBP proteins

directly bind to SYNGAP1 and promote A3SS inclusion. Genetic deletion of Syngap1 A3SS in mice upregulates Syngap1 protein and alleviates the long-term potentiation and membrane excitability deficits caused by a Syngap1 knockout allele. We further report a splice-switching oligonucleotide (SSO) that converts SYNGAP1 unproductive isoform to the functional form in human neurons. This work describes the function of SYNGAP1 A3SS-NMD, the genetic rescue of heterozygous Syngap1 knockout mice, and the development of an SSO to potentially alleviate SYNGAP1-associated haploinsufficiency.

Xiaochang Zhang, University of Chicaco

The schizophrenia-associated 3q29 deletion: Cross-species transcriptional profiling converges on mitochondrial dysregulation

Jennifer Mulle
Rutgers University

JG Mulle[1], RH Purcell[2], E Sefik[2], E Werner[2], AT King[2], TJ Mosley[2], ME Merritt-Garza[2], P Chopra[2], ZT McEachin[2], S Karne[2], N Raj[2], M Robinette[2], ST Warren[2], Z Wen[2], V Faundez[2], SA Sloan[2], GJ Bassell[2]

Mitochondrial dysfunction is increasingly implicated as a contributor to neurodevelopmental and psychiatric phenotypes. The 1.6 Mb deletion on chromosome 3q29 is associated with a staggering 40-fold increase schizophrenia risk. We have interrogated molecular changes using both human cellular and rodent model systems to identify molecular and cellular changes caused by this high-risk variant. We performed single-cell RNA-Sequencing on isocortex from male mice at day p7 (n = 4 WT, n = 4 3q29del mice). We also performed single-cell RNASeq on cortical organoids created from an isogenic 3q29 iPSC line. Organoids were harvested at two developmental time points: day 50 and day 360 (n = 2 WT, 2 3q29del at each timepoint). Using standard pipelines, we compared differentially expressed genes (DEGs) and dysregulated pathways in excitatory neuron clusters across all three experiments. We identified 328 genes that were dysregulated in both mouse and human excitatory neurons (1.9-fold more than expected by chance, p-value 9.5E-38). 94 genes were consistently downregulated across mouse and human (1.9-fold enriched, p-value 1.4E-10) and were enriched for pathways related to oxidative phosphorylation and the aerobic electron transport chain (p-value 8.8E-14). Many of these dysregulated genes are specific to Complex I of the electron transport chain. Functional data in human cellular models of 3q29 deletion syndrome confirm mitochondrial dysregulation. Mitochondrial dysregulation is evident in the schizophrenia-associated 3q29 deletion, converging with results from the 22q11.2 deletion, another genetic variant with exceptionally high risk for schizophrenia. These data suggest the mitochondria may be a target organelle for psychosis risk.

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Poster Session 2

Time: Wednesday, 24/May/2023: 5:30pm · *Location:* Seminar Room in HBB (11 on campus map)

Poster #1. Drosophila Stat92E signaling and behavior following pre-exposure to ethanol.

Emily Petruccelli
Southern Illinois University Edwardsville

Alexandria Wilson[1], Erica Periandri[1], Mackenzie Sievers[1], Emily Nix[1], and Emily Petruccelli[1]

Repeated exposure to ethanol alters neuromolecular signaling and has long-lasting impacts on behavior across taxa. *Drosophila* have been used to model various aspects of Alcohol Use Disorder (AUD), including an escalation in consumption, withdrawal-like behavior, and addiction-like preference for conditioned odor cues. Recent work has implicated the JAK/STAT, a signaling pathway classically associated with development and innate immunity, in AUD. How ethanol exposure impacts STAT activity, and ultimately behavior, is currently unclear. We investigated the role of *Drosophila* Stat92E in ethanol-induced locomotion, STAT transcriptional activity, and splicing of Stat92E isoforms. Expressing *Stat92E-RNAi* increased ethanol-induced hyperactivity in flies previously exposed to ethanol. Repeated ethanol exposure did not significantly alter STAT reporter activity, but repeated exposure tended to change *Stat92E* transcript usage. These findings suggest that the STAT system may be activated under chronic ethanol conditions. Newer work in the lab is focused on establishing assays for ethanol's impact on other complex behaviors such as social spacing and vision-based long-term memories of intoxication. Preliminary data suggest that flies increase clustering behavior after repeated ethanol exposure and that flies develop a conditioned place preference for a blue light cue previously paired with ethanol vapor. Together our work adds to our growing understanding of complex behaviors and translatable models for AUD.

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Poster #2. Effect of Esr1 gene polymorphisms on parental behavior in female mice

Lalitha Devi Mallarapu
National Institute of Genetics

Lalithadevi Mallarapu, Keiko Takanami, Akira Tanave, Yuji Imai and Tsuyoshi Koide

Estrogen receptor 1 (ESR1) is one of the estrogen receptors (ERs) which is encoded by *Esr1* gene. This receptor plays important role in determining several behaviors such as social, sexual, aggression and parental behavior. The expression of ESR1 in hypothalamic medial preoptic area (MPOA) determines the pup retrieval behavior. Previously, it was reported that polymorphisms in *Esr1* gene results in abnormal parental behavior in humans. Here, I addressed how polymorphisms in *Esr1* gene can affect parental behavior in female mice. My study identified that mice from different genetic background, i.e., laboratory strain C57BL/6J (B6) and wild derived strain MSM/Ms (MSM) differ in *Esr1* gene structure. A GCC repeat length polymorphism (9bp) which results in difference of polyalanine repeat numbers was identified in exonic region of *Esr1* gene in MSM when compared to B6. To analyze the role of this "GCC repeat length", we developed an $Esr1^{\Delta 9/\Delta 9}$ mice in which the "9bp" sequence was deleted in B6 mice through CRISPR/Cas9-mediated genome editing. Interestingly, females with heterozygous deletion of "9bp" ($Esr1^{\Delta 9/+}$) showed more severe phenotype than homozygous deletion ($Esr1^{\Delta 9/\Delta 9}$). The low pup (offspring) survival and abnormal parental behavior (reluctant to retrieve pups) was observed in $Esr1^{\Delta 9/+}$ females. Immuno-histochemical analysis of MPOA region, showed lower number of ESR1 positive cells in $Esr1^{\Delta 9/+}$ females when compared with $Esr1^{+/+}$ and $Esr1^{\Delta 9/\Delta 9}$ females. As MPOA ESR1 positive cells are the key mediators of pup approach and retrieval, abnormal maternal behavior of $Esr1^{\Delta 9/+}$ females can be correlated to lower number of MPOA ESR1 positive cells. $Esr1^{\Delta 9/+}$ females showed higher *Esr1* mRNA expression and lower protein levels when compared to wild type control. These results suggest that heterozygous deletion of 9bp in B6 genetic background results in reduced pup retrieval in females. Altogether, this is the first study to reports how *Esr1* genetic polymorphism affects parental behavior in female mice.

Poster #3. Effect of selection for ethanol preference on the transcriptome in the central nucleus of the amygdala of HS-CC mice

Justin Anderson
Portland Alcohol Research Center

JQ Anderson1, P Darakjian1, TJ Phillips1, RJ Hitzemann1, AR Ozburn1

Alcohol use disorder (AUD) is a complex, polygenic disease that has a heritability of about 0.5 for risk. Dysregulation of the transcriptome which precedes exposure to alcohol may contribute to risk for AUD. In this work, we leveraged the genetically diverse HS-CC (heterogeneous stock – collaborative cross) mouse population to perform short term selective breeding for high vs. low ethanol preference, in a two-bottle choice paradigm, to detect changes in the transcriptome associated with ethanol preference. RNA-seq data for the central nucleus of the amygdala for 200 ethanol naïve mice (50/sex/genotype) from selection generation five were used to study differentially expressed genes (DEGs: 2996 genes, FDR < 0.05), differentially variable genes (DVs: 845 genes, FDR < 0.1), differentially wired genes (DWs: 1402 genes, FDR < 0.1), and to construct gene co-expression networks. High-preference network modules enriched in DEGs, DVs, DWs or in highly connected genes not found in the low-preference network were tested for gene ontology enrichment and observed to reproduce data from an earlier set of high and low ethanol preference lines. Ontologies significantly (FDR < 0.05) associated with risk for ethanol preference include: (1) Inflammatory response (*Il34, Il17ra, Trl1, Trl6, Trl13, Dusp1)*, (2) Glutamatergic and GABAergic synapse (*Dlg2, Dlg3, Dlg4, Dlgap2, Dlgap3, Gria3, Grin2b, Gabre, Gabrg1, Gabrq)*, (3) Cilia motility (*Dynah6, Dynah7, Dynah10, Dynah11)*, and (4) Translation and Respiration (*Rps*, Rpl*, Mrps*, Mrpl*, Ndufa3, Ndufa5, Ndufa10, Nduga13)*. These results nominate targets to be considered for manipulation to determine their impact on the development and persistence of alcohol drinking.

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Poster #4. Emergent behavioral and transcriptional properties of pair bonds

Liza Brusman
University of Colorado Boulder

LE Brusman1, AC Fultz2, AK Brar1, ZR Donaldson1,2

Relationships are inherently reciprocal, where the actions of one individual are shaped in real time based on feedback from the other. However, most studies in social neuroscience do not examine both individuals within the same pair, which fails to capture the rich dynamics *between* partners that facilitate relationship success. Socially monogamous prairie voles form pair bonds akin to human relationships, making them an ideal model to study the behavioral and biological elements that comprise organized intra-pair behavior. I previously examined behavior in both members of bonded pairs and found that as bonds mature, a reliable pattern of partner-directed affiliation emerges within pairs. Females show greater levels of partner-directed affiliation and affiliation levels become correlated between partners. To further examine the genetic bases of intra-pair behavior, I examined dyadic interactions and collected nucleus accumbens (NAc) single nucleus RNA sequencing (snRNA-seq) data from paired partners. The NAc is essential for bonding, and transcriptional changes within this region help to maintain pair bonds. Via DeepLabCut and SimBA pipelines, I am identifying the individual and pairwise behavioral sequences that emerge upon bonding. To determine cell type-specific transcriptional changes, I performed single nucleus RNA sequencing (snRNA-seq) on NAc tissue from bonded partners. These data link behavioral patterns and transcriptional state to gain a cellular-level perspective on the neurobiological changes that underlie pair bonds. In sum, my work will provide insight into the emergent fine-grain behavioral sequences, cell type-specific transcriptional changes, and relationships between behavior and transcription that underlie organized intra-pair behavior.

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Poster #5. Identification of Car8 as a novel candidate gene influencing ethanol consumption in Diversity Outbred Mice through transcription in prefrontal cortex

Zachary Tatom

Virginia Commonwealth University

Z Tatom1, MF Miles2,3

While risk for alcohol use disorder has been estimated to be roughly 50% heritable, identifying causal genes and polymorphisms driving this heritability remains difficult. Our lab has recently performed a genetic study on voluntary ethanol-drinking phenotypes across 636 male Diversity Outbred (DO) mice over five weeks of intermittent ethanol access, identifying 3 significant behavioral quantitative trait loci (bQTL). A 90% Bayesian confidence interval for a significant bQTL for last week ethanol consumption spanned only 1 Mbp bQTL on mouse chromosome 4 and contained 11 genes. Top-ranked variants by LOD score did not include any SNPs resulting in coding sequence variation, suggesting a role for regulation of gene transcription. We collected RNA-seq data from 220 prefrontal cortex (PFC) samples from these DO mice, which we analyzed for eQTLs and correlations with ethanol consumption. Of the 11 genes in the chromosome 4 bQTL C.I., only Car8 had a significant cis-expression QTL located near the bQTL and the peak eQTL and bQTL markers were in strong linkage disequilibrium. This gene also had a significant negative correlation between transcript count and last week ethanol consumption (-0.22, p = 0.008) and preference compared to water (-0.23, p = 0.006), and haplotype analysis suggested similar roles for founder strain alleles. Structural equation modeling techniques were then applied to these data to infer directionality and effect size of the observed relationship between transcription and ethanol consumption. These findings suggest a role for transcription of Car8 in prefrontal cortex in modulating voluntary ethanol drinking in DO mice.

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Funding Support: NIAAA P50AA022537

Poster #6. Identifying predictive protein biomarkers for stratification of mental health disorders

Jonathon McLaughlin

Ulster University

Jonathon McLaughlin[1], Coral R. Lapsley[1], Caoimhe Ward[1], Ailis Stevenson[1], Elaine K. Murray[1], Margaret McLafferty[1]

Mental health problems are some of the primary drivers of disability worldwide, presenting a significant socioeconomic burden. Literature has presented an inflammatory driver in the onset of mental health disorders, triggered by environmental and internal stressors. The complex interplay between biological mechanisms and environmental factors means the underlying pathophysiological processes are not fully understood. A cascade of events moderated by the immune system through signaling pathways, results in a distinct inflammatory signature of mental health. The aim of this project is to identify these proteomic, inflammatory signatures to better stratify mental health disorders. Protein levels in plasma were described using the proximity extension assay from Olink, using 6 curated panels, consisting of 529 protein assays. The curated panels included neurological and inflammatory protein assays to identify levels of these proteins in the peripheral plasma. Data was extracted for analysis in R from two separate studies conducted through Ulster University, this analysis included controls (n=40) from both studies, depression (n=32) cases and schizophrenia (n=25) patients. Preliminary results have presented a clear difference of normalised protein expression between depression, schizophrenia and healthy controls. In the depression cohort, a total of 18 downregulated and 15 upregulated proteins were identified, with a total of 12 downregulated and 93 upregulated in schizophrenia patients. Upregulated proteins from both analyses are enriched in immune and inflammatory pathways, with downregulated proteins enriched in different metabolic processes. Results have presented a distinct signature of each disorder, further validation in a larger cohort is required to confidently describe these signatures.

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Poster #7. Investigating the molecular mechanisms of transgenerational effects induced by Ritalin

Rebekah Jolicoeur Alfaro

University of Toronto

RM Jolicoeur Alfaro1, I Anreiter2, H Rodd1

Transgenerational epigenetic inheritance is the transmission of altered phenotypes in the generations beyond those exposed directly or indirectly to a stressor. Stimulant drugs, such as cocaine and nicotine, can induce transgenerational changes, which are associated with alterations in DNA methylation and histone acetylation. Our group previously showed that transgenerational changes in behavior and locomotion were associated with exposure to Ritalin (methylphenidate; MPH), a commonly prescribed stimulant. Exposure of a first generation (G1) of Trinidadian guppies (*Poecilia reticulata*) to Ritalin led to altered phenotypes that were present in the fourth generation (G4). To identify potential mechanisms for this transgenerational transmission of phenotypes, we are investigating the DNA methylation and transcriptomic patterns of several generations. To observe DNA methylation patterns, brains of G4 individuals were sequenced using reduced representation bisulfite sequencing (RRBS). We identified several genes and regions that were differentially methylated between the G4 descendants of G1 control fish and G1 Ritalin-treated fish. In addition, the transcriptomes of G1 brains were investigated to identify genes that were differentially expressed after chronic Ritalin treatment. Several candidate genes were identified from both analyses and qRT-PCR is being used to validate their role in multiple generations. Our study provides insights into the molecular mechanisms underlying Ritalin-induced transgenerational effects on guppy brain function. As the epigenetic effects of

Ritalin exposure have not been previously studied, our results may have important implications for understanding the long-term effects of Ritalin exposure in humans.

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Funding Support: Natural Sciences and Engineering Research Council (Canada)

Poster #8. Investigating the neural ensembles underlying sundowning in an Alzheimer's disease mouse model

Michelle Jin

Int Behavioural and Neural Genetics Society, United States of America

Michelle Jin1 , Holly C. Hunsberger2,6, Alicia Whye3 , Simon Ogundare3 , Nicole Alvarado4, Sophia Sorid3 , Marcos Lanio1 , and Christine A. Denny5,6

As high as 50% of AD patients experience "sundowning" which refers to an increase severity of neuropsychiatric symptoms (NPS), such as agitation, confusion, and anxiety selectively during the evening. Although sundowning significantly influences the decision to institutionalize patients, few preclinical models of sundowning exist and the underlying neural mechanisms are unknown. Here, we establish a behavioral model of sundowning by recording sleep-wake changes in control (Ctrl) and APP/PS1de9 (AD) mice across different ages. Next, we assessed locomotion and exploration behavior in Ctrl and AD mice during the murine evening (sundown) and murine morning (sunrise) using the elevated-plus maze (EPM) and open field (OF) assays. In AD mice but not Ctrl mice, we found there is a significant decrease in the strength of sleepwake rhythms with aging. In the EPM and OF assays, we found that older AD mice (24-monthold males and 12- and 24-month-old females) preferentially explore the open arms and display hyperlocomotion (24-month-old males and 24-month-old females) selectively during sundown. To identify the neural ensembles mediating sundowning, we are combining the ArcCreERT2 x EYFP activity-dependent tagging strategy with a custom analysis pipeline to map brain-wide ensembles differentially active at sundown and sunrise following exposure to the EPM. Overall, we have identified an intriguing time-of-day-dependent behavioral abnormality in an AD model that resembles a "wandering" and agitation phenotype seen in sundowning dementia patients. Our current work identifying the network-level changes between sundown and sunrise ensembles in AD mice will lead more targeted investigations and future therapies for this debilitating syndrome.

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Poster #9. Letrozole treatment alters hippocampal gene expression in common marmosets (Callithrix jacchus)

Melise Edwards

University of Massachusetts Amherst

Melise Edwards[1], Sam Lam[1], Ravi Ranjan[2], Courtney Babbitt[1], Agnes Lacreuse[3]

Aromatase inhibitors (AIs) are a class of drugs commonly given to patients with estrogen receptor (ER)-dependent breast cancers to reduce estrogenic stimulation. However, AIs like Letrozole are associated with negative side effects such as cognitive deficits, sleep disturbances and hot flashes. We have previously shown that these negative effects can be recapitulated in common marmosets (Callithrix jacchus) treated with Letrozole (20 µg daily) for 4 weeks and that Letrozole-treated marmosets show increased levels of estradiol in the hippocampus (Gervais et al., 2019). In order to better understand the mechanisms through which AIs affect cognitive function and increase steroid levels in the hippocampus, we used bulk, paired-end RNA-sequencing to examine gene expression differences between Letrozole-treated (LET; n=8) and vehicle-treated (VEH; n=8) male and female animals. Gene ontology (GO) results show significant reduction across hundreds of categories with some of the most significant being inflammatory response, stress response, MHC Class II protein complex binding, T-cell activation, carbohydrate binding and signaling receptor binding in LET animals ($P < 5.0E-5$). GSEA results show only LET females show enrichment for hormonal gene sets—an effect not observed in LET males. Based on the transcriptional changes observed, we conclude that AIs may differentially affect the sexes in part due to processes mediated by the CYP-450 superfamily. Ongoing studies will further investigate the longitudinal effects of AIs on behavior and whether AIs increase the risk of neurodegenerative stress.

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Poster #10. Neurobehavioral inter-strain variability in response to early life Pb exposure in the recombinant inbred intercrosses

Danila Cuomo

Texas A&M University

Danila Cuomo1 and David Threadgill1

It is well-established that the risk for developing neurological disorders is influenced by the complex interplay of genetics, environment, and gene-by-environment interactions. An environmental factor that has been linked to increased risk of intellectual disability and behavioral disorders is exposure to lead (Pb), which despite the effort to reduce its widespread use, remains a major public health issue. There is no identified safety threshold for Pb, as low-level Pb exposure can determine severe adverse health outcomes in susceptible individuals and late onset of diseases from early life Pb exposure. Epidemiological studies have reported positive associations between genetic factors with Pb sensitivity. However, very few studies have attempted to disentangle their effects on onset of diseases later in life. To model the genetic diversity found in humans, we took advantage of a recombinant inbred intercross mouse population (CC-RIX). F1 males and females derived from crosses of the Collaborative Cross (CC) inbred lines received early life exposure to Pb through lactation until weaning. At about 10-month-old, mice were screened for long-lasting effects from early life Pb exposure to identify neurobehavioral differences and similarities in the twelve CC-RIX lines. We identified significant differences in social behavior, memory and cognition, activity, and anxiety-like behaviors across the strains, indicating that they were either susceptible or resistant to early life Pb exposure. The study highlights the value of the CC-RIX strains for phenotype-genotype associations of many genetic traits that are highly relevant to human Pb-induced neurobehavioral diseases.

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Poster #11. Premorbid addiction model traits and cocaine stimulant sensitivity in spontaneously hypertensive rat (SHR) substrains (Hsd, Crl) bred in-house

Britahny Baskin
Boston University

Britahny M Baskin1,2,3, Hong S Choi3, Carissa J Stots3, Alexandra G Panepinto3, Daniel Schmidlin3,4, Olivia F Barclay3, Kathleen M Kantak3, Camron D Bryant1,2

Psychostimulant use disorders are heritable (40-50%) with a largely unknown genetic etiology. Forward genetic mapping in closely related rodent substrains, termed reduced complexity crosses (RCC) can rapidly identify quantitative trait genes/variants underlying behavior, capitalizing on their near-isogenic nature. We previously observed differences in addiction model traits, including cocaine stimulant sensitivity and operant intraveneous self-administration between spontaneously hypertensive rat substrain (SHR) from either Harlan-Envigo Laboratories (SHR/NHsd) or Charles River Laboratories (SHR/NCrl). Following in-house breeding to remove environmental variance, female and male adult rats were assessed for locomotor activity following saline, and two doses of cocaine (5 and 20 mg/kg; i.p) over two weeks. Rats were also tested on a sucrose preference task for a natural reward and a novelty preference task. Rats then underwent a Differential Reinforcement of Low-Rate Responding (DRL) operant task requiring inhibited responding to earn sucrose pellets and schedule-induced polydipsia (SIP), that assesses habitual and excessive water drinking (models for impulsivity and compulsivity). SHR/NCrl rats exhibited greater locomotor activity when first injected with saline (novelty response) and SHR/NCrl showed greater conditioned hyperactivity in response to saline following repeated (3) injections of cocaine (20mg/kg, i.p). Further, within SHR/NCrl, females exhibited a greater novelty response and greater cocaine-induced locomotion than males with both doses of cocaine, and a greater conditioned effect on saline days following both doses. Alternatively, SHR/NHsd drank more sucrose than SHR/NCrl in the sucrose preference test suggesting substrains differences depending on the type of reward, with female SHR/NHsd drinking more sucrose by body weight than males.

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Poster #12. Rock (pigeon) ‘n’ roll: the genetic basis of rolling in the domestic pigeon (Columba livia)

Atoosa Samani
University of Utah

Atoosa M. Samani1, Emily T. Maclary1, Michael D. Shapiro1

Hereditary rolling or tumbling in the domestic pigeon is an involuntary flight-disrupting behavior characterized by backward somersaults during flight or on the ground. Rolling has excited the curiosity of scholars for centuries; Darwin describes rolling as “…one of the most remarkable inherited habits or instincts ever recorded”. Rolling is progressive: it does not present itself until a few weeks after fledging and becomes more severe with age. Rolling affects locomotion, but no anatomical anomalies are known to be associated with it. Roller pigeons walk, eat, and breed normally, suggesting that rolling is a specific context-dependent behavior and not a generalized neurological disorder. Rolling is recessive and highly heritable, yet the molecular genetic basis remains unknown. Therefore, rolling offers a unique opportunity to discover the molecular basis of a complex yet genetically tractable behavior. Using a combination of quantitative trait locus (QTL) mapping in a laboratory intercross and comparative genomics among pigeon breeds, we identified several loci associated with rolling behavior. Although rolling is a polygenic trait, one major QTL explains 56% of the phenotypic variance in the laboratory cross. Comparisons between the re-sequenced genomes of rollers and non-rollers confirm the polygenic nature of this behavior, and that quantitative genetic and GWAS approaches yield overlapping results. Dissection of the candidate loci at the gene level will deepen our understanding of the molecular basis of involuntary and task-specific movement disorders and other progressive vertebrate behaviors.

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Poster #13. Suppression of mutant HTT partially rescues the neurodegenerative phenotype in the R6/1 mouse model of Huntington’s disease.

Cian Gavin
University College Dublin

Huntington’s disease (HD) is a monogenic neurodegenerative disorder caused by a mutation in the huntingtin (*HTT*) gene. Although HD is often considered a motor disorder, behavioural deficits and cognitive symptoms commonly occur at early stages and are the primary cause of functional decline.

We aimed to explore the therapeutic efficacy of HTT-lowering on behavioural deficits in transgenic HD mice.

R6/1 mice were treated with antisense oligonucleotide (ASO) or vehicle via stereotaxic injection. Treatment was given at either the pre-symptomatic or early-symptomatic disease stage. Mice were subject to a comprehensive battery of behavioural tests to explore the disease phenotype and its potential rescue by gene therapy.

In a test of spatial memory, mice treated with ASO learned to use the optimal spatial search strategy to escape the Barnes maze. However, long-term memory consolidation of escape hole location was not restored. Our data indicates that earlier treatment may be able to restore this deficit when cognitive flexibility is challenged in a reversal learning task. In a novel object test, HTT suppression restored recognition memory. Motor deficits on the rotarod and elevated beam test were also improved by ASO treatment. Finally, data from the elevated plus maze showed that the hypo-anxious phenotype in R6/1 mice was reversed following HTT-lowering.

We show that HTT suppression ameliorates the motor, cognitive and psychiatric symptoms in an acute model of HD. However, the rescue of the neurodegenerative phenotype is only partial. Thus, there remains a need to understand the mechanisms underlying HTT-lowering and its impact on behaviour.

Poster #14. The Estrogen-Immune axis: A key regulator of behavioural inflexibility

Mairéad Sullivan
University College Dublin

Sullivan M1, Macri S2, Ottoman A2, Presta M2, van de Vondervoort I3, Dam S3, Oomen C3, van Heck J3, Glennon J.C 1

Previous analyses of Obsessive-Compulsive Disorder (OCD) highlighted insulin signalling as a causative mechanism, with TALLYHO/JngJ mouse models of Type 2 diabetes demonstrating compulsive behaviour. Here, we aimed to explore how aberrant insulin signalling impacts behaviour via bioinformatic analysis of available OCD GWAS studies, followed by two proteomic validation steps using the Olink Mouse Exploratory Panel and Mass Spectrometry in brain and blood of TALLYHO/JngJ mice vs controls. Significant pathways and networks were identified using Ingenuity Pathway Analysis (Qiagen). Pathway analysis of the human OCD GWAS data and the Olink proteomic validation step converged on the inflammatory Interleukin-17 (Il-17) signalling pathway. Further validation analysis via Mass Spectrometry similarly highlighted immunity-based changes. We next sought to identify upstream regulators that govern this inflammatory-behaviour axis in diabetes. Pairwise analysis was performed between inflammation-related somatic disorders that feature comorbid compulsivity and/or anxiety (Psoriasis, Crohn's, Ulcerative Colitis, IBS) vs disorders of behavioural inflexibility (Autism, OCD, Depression, Anxiety). Beta-estradiol appeared as the most significant recurring upstream regulator, with comparison of associated regulatory networks from the above disorders of behavioural inflexibility and TALLYHO/JngJ proteomic data showing recurrence of an estrogen - Il-1beta link, a cytokine that promotes neuroinflammation. Administration of metformin, a Type 2 diabetes medication, to compulsive TALLYHO/JngJ mice was found to improve aspects of their behavioural symptomology, with mass spectrometry analysis of blood and brain confirming resolution of neuroinflammatory factors. We conclude from this that dysregulated immune mechanisms may be responsible for insulin-mediated behavioural abnormalities, with estrogen signalling playing a regulatory role.

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Poster #15. Ultrasonic vocalization syllable composition during neonatal opioid withdrawal in FVB and BALB/c substrains and CFW outbred mice

Kelly Wingfield

Boston University School of Medicine

Kelly Wingfield1,2, Kayla Richardson1,3, Teodora Misic1,4, Nalia Abney1,4, Kaahini Jain1,4, Jacob Beirle1,2, Emily Yao1, Camron D. Bryant1,4

Opioid use during pregnancy is a growing public health concern, as gestational opioid exposure often leads to neonatal opioid withdrawal syndrome (**NOWS**) in infants. Current treatments for NOWS involve opioid replacement therapy with methadone or buprenorphine, and interventions promoting maternal care. We use a mouse model of NOWS to assess several phenotypes during spontaneous morphine withdrawal (16hr) on P7 and P14, including ultrasonic vocalizations (**USVs**) and locomotor activity, and nociceptive testing. We found that neonatal morphine exposure alters the USV profile, as demonstrated by a significant increase in the proportion of "Complex 3" syllables during withdrawal on P14. The increase in Complex 3 was observed in three inbred FVB substrains, as well as the outbred CFW stock. We also administered naloxone to morphine naïve FVB pups and saw an increase in Complex 3. These data suggest that Complex 3 syllables may be a potential marker for the aversive state of opioid withdrawal in mice. On P16, we collected brainstem tissue for RNA sequencing and found an upregulation of the kappa opioid receptor (**KOR**) transcript *Oprk1*. Given the kappa system's involvement in dysphoria associated with opioid withdrawal, we hypothesize that dynorphin-mediated activation of KOR increases Complex 3 emission. In a separate experiment, on P15 we administered the KOR antagonist, nor-BNI, and recorded USVs. Thus far, we have not observed a reduction in USVs or Complex 3 syllables following nor-BNI treatment, but plan to repeat the experiment with different experimental parameters. We are also testing additional substrains (BALB/c) and genetic *Zhx2* mutants, which is a transcriptional repressor that regulates brain metabolite concentration of opioids.

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Poster #16. Characterization of transcriptome differences in a Taar1 knock-in model of high vs. low voluntary methamphetamine intake

Tamara Phillips

Oregon Health & Science University

T.J. Phillips[1,2], C. Reed[1], H. Baba[1], P. Darakjian[1], R. Hitzemann[1]

A mouse selective breeding project identified a spontaneous mutation in the trace amine-associated receptor 1 (*Taar1*) gene that accounts for 60% of the genetic variance in voluntary methamphetamine (MA) intake in the high (MAHDR) and low (MALDR) MA drinking lines. MAHDR, which are *Taar1*$^{m1J/m1J}$ homozygotes, consume binge levels of MA, whereas MALDR, which possess the wild type allele (*Taar1*$^{+}$) avoid consuming MA. Knock-in of the *Taar1*$^{+}$ allele in MAHDR mice, resulted in low MA intake. To examine transcriptome differences, RNA was extracted from nucleus accumbens (NAc), ventral midbrain (VMB), and prefrontal cortex (PFC) samples of MA-naïve knock-in and control line mice (n=15-17/genotype) and submitted for RNA-Seq analysis. In the NAc, VMB and PFC, there were 2107, 541 and 461 differentially expressed (DE) genes, respectively. Protein coding genes were included in a gene ontology analysis that has been completed for the NAc, where there was the largest number of DE genes. For that region, 1148 genes were up-regulated and 959 were down-regulated in KI compared to control mice. Gene ontology results revealed alterations in translation, mitochondrial function, and energy homeostasis. Overlap of these results with data for NAc DE for the MAHDR and MALDR lines was next examined. Three genes were shared in common: *Psmb6*, *Pcdhgb6*, and *Map7*. All are members of biological systems that have been implicated in methamphetamine effects. Genes that overlap in these two data sets may implicate the effect of *Taar1* variation on MA intake and be good candidate genes for novel therapeutic exploration.

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Poster #17. Co-housing rats discordant for a neurobehaviorally significant neonatal exposure to the general anesthetic sevoflurane affect each other's neurobehavioral outcome

Anatoly Martynyuk

University of Florida

L-S Ju1, TE Morey1, N Gravenstein1, CN1 Seubert, B Setlow2,3, AE Martynyuk1,3

Human studies compared neurocognitive outcomes in twins, in which one, both, or neither of the twins underwent procedures that involved exposure to general anesthetics. Because exposed and unexposed members of a twin pair had an equally poor

neurocognitive outcome the studies concluded that pre-existing conditions rather than general anesthetics were the cause. We tested in healthy rats whether sevoflurane-unexposed rats that were reared together in the same litter/cage with sevoflurane-exposed rats can develop behavioral deficiencies similar to those developed by their exposed cagemates. Postnatal day (P) 5 male Sprague-Dawley rats from different litters were mixed and randomized to new litters consisting of: 1) pups that underwent exposure to 2.1% sevoflurane for 6 h on P5 (SEVO); 2) unexposed (Control); and 3) equal numbers of sevoflurane-exposed and unexposed pups (MIXED). After weaning, rats from the same litter were housed two/cage, with an unexposed/exposed pair from the MIXED litters. They were evaluated between P60 and P100. As in prior studies, the SEVO rats exhibited deficiencies at gene expression, stress response and behavior levels. The MIXED sevoflurane-exposed and -unexposed rats were indistinguishable at all these levels. The Mixed-sevoflurane rats, compared to the SEVO rats, showed less anxiety-like behavior, had similarly impaired sensorimotor gating and exacerbated corticosterone responses to stress, and unaffected spatial memory. Our findings suggest that through cohabitating, rats can affect each other's brain development, ameliorating some sevoflurane-induced deficits in exposed rats, and inducing some of these deficits in unexposed rats. These findings may have broad implications for basic and clinical neuroscience.

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Funding Support: NICHD R56 HD102898, NICHD R01 HD107722, the I. Heermann Anesthesia Foundation and the JH Modell Endowed Professorship (USA)

Poster #18. Effects of Chronic Unpredictable Stress on behavioral outcomes in C57BL/6J and DBA2/J mice.

Melloni Cook
University of Memphis

Melloni N. Cook and Chris Hartless

Stress is a contributor to poor health outcomes- both physical and mental. Stress during early life, in particular, can influence these outcomes. Animal models have been useful in understanding how stress can affect a wide array of outcomes. The chronic unpredictable stress paradigm (CUS), which may be similar to the unpredictable nature of stressors humans experience, has been useful; however, few studies have taken full advantage of examining sex- and genetic-factors. We have exposed adolescent male and female C57BL/6J (B6) and DBA2/J (D2) mice to four weeks of CUS followed by behavioral testing in a test battery. Preliminary results indicate that CUS increased anxiety-related behavior of B6 mice in the elevated-zero maze but had little effect in D2 mice. In contrast, CUS decreases anxiety-related behavior in D2 mice in the light/dark tests with little effect in B6 mice. In either test, anxiety-related behaviors were not related to any CUS effects on activity. There was no effect of CUS on open field behaviors in either strain. There was no CUS effect on acoustic startle response, however, B6 mice and D2 females exposed to CUS had increased prepulse inhibition (PPI) while D2 males showed reductions in inhibition at 70 dB. For CUS had no effect on PPI in B6 or D2 females at 85 dB but increased inhibition in B6 males and decreased inhibition in D2 males. These results suggest that the effects of CUS can be influenced by genetic factors but are also sex and task dependent.

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Poster #19. Elevated mRNA expression and activity of Toll-like receptor and cytokine in patients with schizophrenia.

Saahithh Redddi Patlola
University of Galway

Saahithh Redddi Patlola1, Laurena Holleran2, Akhil Konkoth1, Daniel Kerr1, Gary Donohoe2, Declan McKernan1.

Schizophrenia is a psychiatric disorder with a complex aetiology. There has been a growing interest in the role of Toll-like receptors (TLRs) and cytokines in the pathophysiology of schizophrenia. TLRs are pattern recognition receptors primarily involved in immune mediation. We aim to investigate if there is an altered expression and activity of peripheral cytokines and TLRs in patients with schizophrenia. A total of 279 participants were included in this study. We used high-sensitive ELISA kits to detect the peripheral levels of cytokines in the plasma of both healthy volunteers (N=189) and patients with schizophrenia (N=90). Whole blood was stimulated with TLR2-4 agonists to investigate cytokine activity. cDNA synthesised from purified mRNA (whole blood) was used to perform qRT-PCR to analyse the relative expression of cytokines and TLRs. Results from ELISAs show significantly elevated levels of IL-6, IL-8, IL-10, TNF-a and CRP ($p < 0.01$) but not IL-12 and IFN-g in patients with schizophrenia compared to controls. Significant higher levels of IL-6 and IL-8 in patients were observed post TLR2 and TLR4 receptor stimulation. The mRNA expression analysis illustrated a significant higher expression of IL-6 (1.3-fold, $p<0.06$) and IL-8 (1.44-fold, $p<0.001$) and not with TNF-a. A significant upregulation in the mRNA expression of TLR2 (1.1-fold, $p<0.05$) and TLR4 (1.3-fold, $p<0.01$) was observed but not with TLR3. These results suggest that patients with schizophrenia show altered inflammatory activity. They also point in the direction of possible role of toll-like receptors in the mediation of neuroinflammatory response in schizophrenia.

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Poster #20. Fully automated longitudinal ethology from home cage tracking: quantifying age-related behavioural differences in BXD mice

Rupert Overall
Humboldt University of Berlina

DM Glikman 1, J Musolf 1, Y Winter 1, RW Williams 2, RW Overall 1

Our combination of the ColonyRack RFID-based home cage tracking hardware with the open-source ColonyTrack analysis software now enables behavioural monitoring at unprecedented resolution. This system offers a phenotyping depth of currently 21 informative metrics, a sampling width of potentially hundreds of mice tracked together in a colony and longitudinal data limited only by the animals' lifespan. Continuous tracking enables temporal patterns, such as age-related activity fragmentation, to be discovered. The scalable colony size means that social interactions can also be measured. The breadth of data collected, including activity, exploration and social metrics, means that a multiparametric status of each animals can be calculated and changes in these scores over time can be observed. We have used this system to follow cohorts of aged BXD mice through some of the last months of life and identified several heritable features of late-life behaviour. Ongoing work is extending the system even further, both in terms of phenotyping detail as well as scalability.

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Poster #21. Homeotic modulation of a sexually dimorphic neural circuit

Nicole Leitner
Washington University in St. Louis

Nicole Leitner and Yehuda Ben-Shahar

Segmental specializations of neuronal morphology and physiology along the anteroposterior adult brain axis play a fundamental role in locomotion, cognition, and behavior. However, the genetic and molecular mechanisms that drive segment-specific differentiation of homologous neurons remain poorly understood. Therefore, we propose the hypothesis that segmental neuronal specializations are driven via segment specific interactions between canonical neuronal differentiation pathways and homeotic segment identity factors. To test this hypothesis, we investigate how genetic interactions between the homeotic factors that determine thoracic segment identity and the canonical neuronal sex determination pathway drive the segmental specializations of pheromone-sensing neurons in adult legs that express the ion channel *pickpocket23* (*ppk23*). Specifically, we focus on one important morphological feature, the axonal midline crossing decision. We show that the axons of *ppk23*-expressing neurons cross the midline of the of the ventral nerve cord (VNC) in males but not in females, while those in the meso- (T2) and metathoracic (T3) legs do not cross the midline in both sexes. Furthermore, we present evidence that this T1 segment specific polymorphism is regulated via an interaction between the non-cell-autonomous action of the homeotic gene *Sex combs reduced* (*Scr*) and the cell-autonomous action of the male specific neuronal differentiation factor *fruitless* (*fru*). Based on these data, we propose a model which stipulates that *Scr* promotes axonal midline crossing in the prothoracic VNC by unmasking fru^{M}-dependent regulation of cell-autonomous neuronal signaling pathways that regulate the axonal midline crossing decision.

Washington University in St. Louis

Poster #22. Identification of chromosomal regions associated with susceptibility or resistance to absence epilepsy performed in a double mouse model derived from a bidirectional genetic selection

Benoit Martin
LTSI - INSERM U1099

B Martin[1], G Dieuset[1], V Latapie[2], S Jamain[2]

Absence seizures are a common form of generalized genetic epilepsy characterized by bilateral and synchronous spike-wave discharges (SWDs). Our long-term goal is to identify genes that are positively or negatively involved in the regulation of absences epilepsy. In the shorter term, we have carried out a mapping study to identify chromosomal regions associated with the manifestation of SWDs using an innovative double mouse model. On the other hand, it turns out that our double mouse model also represents a model of seizure under β-carboline. Therefore, we have similarly performed a mapping study for this trait in addition to the one performed for absence-epilepsy . In fact, our study uses a double mouse model for absence-epilepsy , consisting of two lines derived from a bidirectional selection. The first line (BS/Orl) spontaneously expresses SWDs characteristic of murine absence-epilepsy. On the contrary, the other line (BR/Orl) does not show SWD even under the influence of SWD-inducing agents. The BS/Orl line thus represents a model of epilepsy-absence susceptibility while the BR/Orl line represents a model of resistance. We created two segregating populations F2 (BR.BS F1 x BR.BS F1) and N2 (BR.BS F1 x BS) from the BS/Orl and BR/Orl lines. These two populations were tested for spontaneous SWD activity and DMCM-induced seizures susceptibility and genotyped for over 143,000 polymorphisms using Illumina GeneSeek Genomic Profiler Mouse arrays. In this way, based on LOD-scores calculations, we constructed probability maps of the presence of genes related to epilepsy-absence susceptibility or resistance as well as β-carboline susceptibility.

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Poster #23. Methylome profiling of young adults with depression

Elaine Murray
Ulster University

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Many mental health problems, including depression, often emerge before age 18 and there is growing concern about the high numbers of college students with mental disorders. We conducted the Ulster University Student Wellbeing Study and Student Psychological Intervention Trial as part of the WHO International College Student Project and indeed found alarmingly high rates of mental disorders among first year students, with over 25% having experienced depression. Genetic and environmental factors have been linked to increased risk for depression and DNA methylation may represent one mechanism through which environmental risk factors can mediate the biological changes associated with depression. This study compared genome-wide DNA methylation patterns in saliva-derived DNA from individuals with depression (n=250) and matched healthy controls (n=250) using the Illumina EPIC (850k) array. FDR-significant differential methylation was identified at several CpG sites across the genome. Gene ontology analysis of gene bodies and promoters with the largest change in methylation indicated highly significant enrichment for immune response. In summary, depression is associated with significant effects on DNA methylation, and the genes most affected are related to immune function, consistent with the accumulating evidence supporting a relationship between inflammation and depression. Additionally, DNA methylation changes at key loci, detected in saliva, may represent a valuable tool for identifying at-risk subjects.

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Poster #24. Neuroinflammatory Pathways in the Midcingulate Cortex in Huntington's Disease

Andrea Kwakowsky
University of Galway

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Huntington's disease (HD) is an autosomal dominant genetic neurodegenerative disorder that can result in variable symptoms including the loss of motor control, behavioural and psychiatric symptoms, and cognitive decline. HD pathophysiology has been linked to neuroinflammation – the presence of inflammatory mediators and reactive glial cells in the brain parenchyma. Many signaling pathways likely interact to propagate neuroinflammation in the brain. Neuroinflammation is thought to cause cell loss, and cell loss in

the anterior cingulate cortex is linked to HD mood symptoms. The presence of neuroinflammation in the HD midcingulate cortex (MCC) has not yet been investigated.

We studied neuroinflammatory pathways in 14 HD and 9 control post-mortem human MCC samples using mRNA sequencing. HD cases were split into the symptom profiles of motor, mood and mixed. This data was analysed using Gene Ontology (GO) enrichment analysis.

We found 24 upregulated inflammation-related genes including toll-like receptors, classical complement, AQP4, CHI3L1, P2X7R, S100A9 and SPP1 across HD cases. However, 13 inflammation-related markers including chemokines were downregulated. GO enrichment analysis reflected this, with multiple inflammation-related GO terms being upregulated and downregulated in HD. In mood HD cases, 7 inflammation-related genes were upregulated, and none were downregulated.

These results present a complex picture of potential inflammation priming in the HD MCC, rather than overt neuroinflammation.

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Poster #25. Role of GSCAN Identified Genes in the Astrocytic Response to Nicotine

Andrew Lombardi

Int Behavioural and Neural Genetics Society, United States of America

Andrew Lombardi1, Myra Bower1, Curtis Borski1,2, Kora Kastengren1,2, Marissa Ehringer1,2, Jerry Stitzel1,2, Charles Hoeffer1,2

Improved understanding of nicotine neurobiology is needed to reduce or prevent chronic addiction, the detrimental effects of nicotine withdrawal, and increase successful cessation of use. Nicotine use Genome wide association studies (GWAS) suggest an astrocytic role for nicotine responses. Previously, we found that *Akt2* expression is restricted to astrocytes in mice and humans and may play a role in the nicotinic responses of astrocytes. The current study aims to identify additional astrocyte-expressed genes that alter nicotine's effect on astrocytes and contribute to nicotine use behaviors. To identify genes of interest (GOI)s, we selected genes from TWAS results from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) significantly associated with cigarettes per day (CPD) and smoking cessation (CS) that were also expressed in human and mouse astrocytes. The genes that met these criteria were further prioritized by whether they also were associated with CPD and SC in additional analyses including Pascal, DEPICT, and fine mapping. Using a CRISPR approach to knockdown GOI expression, we are screening 25-50 of these smoking-related, astrocyte-expressed genes. Using area analysis, we are assessing the role of the GOI on astrocyte size and morphology in primary mouse astrocyte cultures following nicotine treatment. The screen will identify GOIs for generating new mouse models to assess the role of the astrocyte-expressed gene on nicotine behaviors and *in vivo* astrocyte response to nicotine. These results will allow for the identification of potential novel drug targets and will improve the current understanding of the astrocytic response to nicotine.

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Funding Support: R21 DA055781 (Ehringer, Hoeffer, Stitzel; MPIs)

Poster #26. Serial Reversal Learning in an Olfactory Discrimination Task in 3xTg-AD Mice.

Richard Brown

Dalhousie University

Kyle M Roddick, Heather M Schellinck, Richard E Brown

The 3xTg-AD transgenic mouse model of AD develops both amyloid-β plaques and tau tangles by 6 months of age. We tested male and female 3xTg-AD mice (n=15), and their B6129 wildtype controls (n=18), between 5 and 24 months old on a series of 18 two- odour (S+ vs S-) discrimination and reversal tasks on a go, no-go procedure in an operant olfactometer. Mice were trained until they achieved a criterion of 85% correct in odour discrimination and in the reversal task, and then a new odour pair was presented until the mice had completed a series of 18 discriminations and reversals. All mice made more errors learning the reversal tasks than the discrimination tasks. However, many mice showed near errorless learning, making one or fewer errors on some odour discriminations and reversals. There was a significant genotype effect with the 3xTg-AD mice showing more instances of near errorless learning than the B6129 mice. When retested for long-term memory on the final odour pair 1 - 3 months after the final reversal learning task, there was no genotype difference, as all mice made more errors than when first presented with this odour pair. The high level of performance, including the near errorless learning, suggests that both the WT and 3xTg-AD mice were able to develop a learning-to-learn strategy for both odour discrimination and reversal learning. Olfactory learning and memory show no disruption the 3xTg-AD mice.

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Poster #27. The effect of genetic risk for schizophrenia on cognitive performance

Shir Dahan

University of Galway

S Dahan 1, G Donohoe 2

Genetic risk, childhood trauma, and inflammation have been associated with cognitive impairments in schizophrenia. This study aimed to test whether schizophrenia polygenic risk score (i.e., an estimate of genetic liability for schizophrenia) would predict performance in episodic memory, emotion recognition, and theory of mind. Furthermore, the study aimed to find if this relationship would be mediated by the pro-inflammatory cytokine interleukin 6 and if childhood trauma and physical neglect would moderate this relationship such that it would be stronger if childhood trauma or childhood physical neglect occurred. A polygenic risk score was calculated for each of the 104 schizophrenia patients and 206 healthy participants. Cognitive functions were measured with a battery of cognitive tests. Childhood trauma and physical neglect were measured with the Childhood Trauma Questionnaire. Interleukin 6 was measured in plasma and in stimulated toll-like receptors whole blood. Linear regression showed that schizophrenia polygenic risk score predicted episodic memory but not social cognition performance. Simple mediation analysis revealed that interleukin 6 did not mediate the relationship. Simple moderation analysis revealed that childhood trauma moderated the relationship between schizophrenia polygenic risk score and verbal episodic memory. Physical neglect moderated the relationship of schizophrenia polygenic risk score with episodic memory and theory of mind. These findings are consistent with previous studies, where episodic memory performance was predicted

by microglia and complementbased schizophrenia polygenic risk scores. However, the results are inconsistent with findings that suggest genetic liability for schizophrenia is related to social cognition. Moderation findings support the gene-environment interaction hypothesis. Genetic susceptibility to environmental risk factors might lead to dysregulation of developmental agents at crucial stages and thus cause cognitive impairments.

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Poster #28. MEF2C Dysregulation and its Association with Neuropsychiatric Disorders and Cognitive Function in Human Neural Cells

Ali Deema
University of Galway

Deema Ali[1] and Derek W. Morris[1]

Myocyte Enhancer Factor 2C (MEF2C) is a transcription factor that plays a crucial role in neurogenesis and synapse development. Genetic studies have identified MEF2C as a gene that influences cognition and risk for neuropsychiatric disorders, including autism spectrum disorder (ASD) and schizophrenia (SCZ). Here, we investigated the involvement of MEF2C in these phenotypes using human-derived neural stem cells (NSCs) and induced neurons (iNs), which represented early and late neurodevelopmental stages. For these cellular models, MEF2C function had previously been disrupted, either by direct or indirect mutation, and gene expression assayed using RNA-seq. We integrated these RNA-seq data with MEF2C ChIP-seq data to identify dysregulated direct target genes of MEF2C in the NSCs and iNs models. Several MEF2C direct target gene-sets were enriched for SNP-based heritability for intelligence, educational attainment and SCZ, as well as being enriched for genes containing rare *de novo* mutations reported in ASD and/or developmental disorders. Analysis of single-cell RNA sequencing data revealed that several excitatory glutamatergic neurons in the hippocampus and cortex, including deep layer pyramidal cells, CA1 principal cells, and entorhinal cortex, were enriched for MEF2C direct-target genes. Overall, our results suggest that genes dysregulated as a consequence of either direct or indirect MEF2C disruption contribute to SCZ development and cognitive function from early stages of neurodevelopment. These genes are involved in a wide range of biological processes including neural/glial cell differentiation, cell migration, protein modification and catabolism in NSCs, as well as mitochondrial function and energy production in iNs.

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Poster #29. Evaluation of a pumilio gene epitope tag in a genomic context as an isomorphic allele in Drosophila using modification of behavior and activity of bang senseless

Rudolph Bohm
Texas A&M University

S Bakhati1, MM Cruz1,2, DM Delancy1, RA Bohm1

pumilio, isolated as a modifier of a *paralytic* hypermorphic allele, is a translational regulator that binds RNA. Its post-transcriptional gene regulation plays a role in embryogenesis, eye development, neuronal excitability and long-term memory. Mutations in the human homology cause neuro-degerative diseases. Using CRISPR, we epitope tagged this gene in a common exon in to explore interactions and localizations of the gene. The tagged region is in a low complexity domain that is relatively non-conserved and we strove to create a tag without creating a partial loss of function. We use a behavioral readout to place this new tagged allele in an allelic series and describe it by modifying a gene that it interacts with genetically: *bang senseless* (*bss*). Our poster will report our latest findings.

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Symposium 5: The role of inflammation in psychosis

Time: Thursday, 25/May/2023: 9:00am · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Declan McKernan
Session Chair: Sinead King

The role of inflammation in psychosis

Declan McKernan
University of Galway

Symposium Chairs: Declan McKernan and Gary Donohoe

Symposium Abstract:

The nervous and immune systems are closely intertwined with interactions occurring at a number of levels. Neuroinflammation is an inflammatory response within the central nervous system involving neurons, glia and immune cells. In recent years, there has been a growing interest in the role of neuroinflammation in the pathophysiology of neurological and psychiatric disorders. Many genetic loci associated with inflammatory processes have been strongly linked to increase risk for neurological and psychiatric conditions such as schizophrenia. Neuroinflammation is also robustly associated with changes in behaviour in animal models of schizophrenia. Inflammatory mediators have been shown to be dysregulated (mostly elevated) across human studies, post-mortem studies and animal studies, and immune cell irregularities noted both in the brain and in other parts of the CNS. Recent findings also suggest that there is significant variation in such disorders depending on age, sex and environmental factors. As a consequence, neuroinflammation has become a target of interest for therapeutic intervention in such disorders. This symposium aims to share recent advances in immunogenetics, brain imaging and cognition, cytokine signalling and the effects of other immune molecules in the nervous system that can enhance our understanding of psychiatric disorders, as well as their prevention and treatment. Talks will present data from clinical studies involving patients with psychosis as well as relevant animal studies.

Genetic, early environment and cognitive function in schizophrenia: the mediating role of inflammation

Sinead King
University of Galway

Gary Donohoe1,2*Emma Corley1,2, Saahithh Redddi Patlola2,3, Aodán Laighneach2,4, John P Kelly3, Declan P Mckernan3, Sinead King1,2, Brian Hallahan5, Colm Mcdonald5, Derek W Morris2,4

Lower cognitive function is associated with poorer physical and mental health, and in psychosis is strongly predictive of lower social and occupational function. In a series of recent studies we have sought to model the associations between common genetic variation, childhood trauma, immune response, and cognitive function, using both large-scale datasets (ALSPAC and UKBB) and the iRELATE study of patients and healthy participants. Summarising the findings from these studies we provide evidence that (a) both common genetic variation and early childhood trauma predicts variation in cognitive performance, (b) that childhood trauma moderates the pathway between common genetic variation, brain structure, and cognition, and (c) that increased inflammatory response (as measured by IL-6) mediates the effects of childhood trauma on cognitive function both in its own right and when considered sequentially along with cortical measures of functional connectivity. We conclude that childhood trauma has an important deleterious effect on cognitive function, and in so doing is likely to moderate the effects of common genetic variants associated with both cognition and schizophrenia. We further speculate that these effects are themselves mediated via inflammatory response both directly and indirectly via deleterious effects on cortical connectivity.

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Genetic and inflammatory effects on childhood trauma and cognitive functioning in patients with schizophrenia and healthy participants

Emma Corley
University of Galway

Emma Corley[1,2], Saahithh Redddi Patlola[2,3], Aodán Laighneach[2,4], Aiden Corvin[5], Ross McManus[5], Marcus Kenyon[5], John P Kelly[3], Declan P Mckernan[3], Sinead King[1,2], Brian Hallahan[6], Colm Mcdonald[6], Derek W Morris[2,4], Gary Donohoe[1,2*]

Background: Recent studies have reported a negative association between exposure to childhood trauma, including physical neglect (PN), and cognitive functioning in patients with schizophrenia. Childhood trauma has been found to influence immune functioning, which may in turn contribute to risk of schizophrenia and cognitive symptoms of the disorder. The purpose of the present study was to test the hypotheses that (a) a combined latent measure of inflammatory response would mediate the association between physical neglect and cognitive ability and that (b) higher genetic risk for schizophrenia would moderate this association. **Methods:** A total of 279 participants (102 patients with SCZ and 177 healthy controls) were included in this study. Mediation and moderation analyses were performed using structural equation modelling. The latent variable of inflammatory response was indexed using basal plasma levels of IL-6, TNF-α and CRP. Cognition was assessed across three domains including full-scale IQ, logical memory and the emotion recognition task**. Results:** Significant indirect effects of the latent variable of inflammation were found across all SEM models, such that the inflammatory marker fully mediated the associations between physical neglect and cognition. When genetic risk for schizophrenia was included as a moderator in the model, this was observed to significantly moderate the direct relationship between physical neglect and logical memory ($\beta_{indirect}$= -0.244, CI= -0.388 to -0.101, p <0.001) and between physical neglect and full-scale IQ ($\beta_{indirect}$= -0.154, CI= -0.298 to -0.010, p = 0.038). **Conclusion:** Increased inflammation and higher genetic risk for SCZ represent an important mechanism linking adverse early experiences to later cognitive deficits in patients with SCZ and healthy participants.

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Social isolation-induced transcriptomic changes in mouse hippocampus impact the synapse and show convergence with human genetic risk for neurodevelopmental phenotypes

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Early life stress (ELS) can impact on how the brain develops and is a risk factor for neurodevelopmental disorders such as schizophrenia. Post-weaning social isolation (SI) is used to model ELS in animals, using isolation stress to disrupt a normal developmental trajectory. We aimed to investigate how SI affects the expression of genes in mouse hippocampus and to investigate how these changes related to the genetic basis of neurodevelopmental phenotypes. C57 BL/6J mice were exposed to post-weaning SI (PD21-25) or treated as group-housed controls (n = 7-8 per group). RNA sequencing was performed on tissue samples from the hippocampus of adult male and female mice. Four hundred and 1,215 differentially-expressed genes (DEGs) at a false discovery rate (FDR) of < 0.05 were detected between SI and control samples for males and females respectively. DEGS for both males and females were significantly overrepresented in gene ontologies related to synaptic structure and function, especially the post-synapse. DEGs were enriched for common variant (SNP) heritability in humans that contributes to risk of neuropsychiatric disorders (schizophrenia, bipolar disorder) and to cognitive function (IQ). DEGs were also enriched for genes harbouring rare de novo variants that contribute to autism spectrum disorder and other developmental disorders. Finally, cell type analysis revealed populations of hippocampal astrocytes that were enriched for DEGs. Overall, these data suggest a convergence between genes dysregulated by the SI stressor in the mouse and genes associated with neurodevelopmental disorders and cognitive phenotypes in humans.

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Inflammation and Brain Structure in Schizophrenia: Evidence from longitudinal cohort data, mendelian randomisation and machine learning

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JC Rogers 1, 2, E Palmer 1, I Morales-Munoz 1, BI Perry 3, JA Williams 4,5,6, SL Griffiths 1, A Murray 1, PA Lalousis 1,2, B Deakin 7, MZUH Katshu 8,9, P Liddle 8, GM Khandaker 10,11, R Upthegrove 1,2,12

Evidence suggests a key role between inflammation and schizophrenia, with increased circulating concentrations of proinflammatory cytokines and acute phase proteins including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF)-α, and C-reactive protein (CRP) thought to be key mediators of the onset of illness. However, whilst the extant literature supports associations between systematic inflammation and schizophrenia, a causal link between immune-dysfunction and psychosis is yet to be established. Evidence of a longitudinal relationship; exposure before the outcome, can help increase evidence to causality. Using longitudinal birth cohort data, latent-class growth analysis identified different inflammatory trajectories across childhood and adolescence. Prospective associations between raised levels of inflammation (blood-based CRP) and mental health outcomes at age 24 revealed a divergent group with persistently raised levels of CRP (peak at age 9) who were four times more likely to develop psychosis. Potential causal associations between inflammation and brain structure have also been explored using mendelian randomization in a large population dataset. Results revealed that genetically predicted levels of IL-6 were associated with changes in brain structure within cortical regions implicated schizophrenia. Building on this work, we used semi-supervised machine learning to identify distinct sub-groups of patients with schizophrenia based on divergent inflammatory, clinical and neuroanatomical profiles. Four schizophrenia-specific clusters that were separable from controls were identified with increased CRP, IL-6, TNF-α and non-inflamed subgroups associated with differences in clinical symptoms and reduced brain volume. Results suggest a key role of inflammation in the development of psychosis with inflammatory subgroups potentially informing stratification, treatment and aetiology.

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Inflammation in psychosis: A potential role for Toll-like receptors

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Psychosis is a psychiatric disorder with a complex aetiology. Neuroinflammation is an inflammatory response within the central nervous system involving neurons, glia and immune cells. Many genetic loci associated with inflammatory processes have been strongly linked to increase risk for neurological and psychiatric conditions such as schizophrenia. Neuroinflammation is also robustly associated with changes in behaviour in animal models of schizophrenia. Inflammatory mediators have been shown to be dysregulated (mostly elevated) across human studies, post-mortem studies and animal studies, and immune cell irregularities noted both in the brain and in other parts of the CNS. Levels of these mediators appear to influence cognitive performance. Levels can also be altered by anti-psychotic medication. Recent findings also suggest that there is significant variation in such disorders depending on age, sex and environmental factors. As a consequence, neuroinflammation has become a target of interest for therapeutic intervention in such disorders. Toll-like receptors are pattern recognition receptors primarily involved in mediating inflammatory responses centrally and peripherally. These receptors are widely expressed and are responsible for the In this study, we report recent findings from a human

study involving patients with schizophrenia (n=90) and health controls (n=189). Results show a significant alteration in the expression levels of key Toll-like receptors on peripheral blood cells as well as the resulting release of cytokines from stimulating whole blood ex vivo. We also discuss how these findings are potentially influenced by environmental factors and how they might potentially influence variation in cognitive performance.

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Selected Talks 3

Time: Thursday, 25/May/2023: 11:30am · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Dara Cannon
Session Chair: William Lynch

Novel genetic associations for problematic alcohol use show sex-specific and pleiotropic effects in mutant mouse models

Amanda Barkley-Levenson
University of New Mexico

A.M. Barkley-Levenson1, D-J.G. Paredes1, A.L Silva Borges2

Recent large, well-powered human genome-wide association studies have identified numerous novel genetic variants associated with alcohol consumption and problematic alcohol use. Mutant mouse lines provide a first step to determine whether individual gene manipulations are sufficient to alter alcohol intake and related phenotypes, and to begin to explore potential underlying mechanisms of action. Here, we used knockout mouse lines and a variety of drinking procedures and other behavioral phenotypes to investigate three genes (*Fut2, Dpp6,* and *Slc39a8*) that have been associated with problematic alcohol use and/or alcohol consumption in humans. We found that the patterns of results displayed high variability across different mutant lines, with evidence of possible sex-specific and pleiotropic effects. *Fut2* homozygous knockout mice showed increased binge-like ethanol drinking in males only, but did not differ from wildtype animals on ethanol preference or total alcohol intake during an intermittent access two-bottle choice procedure. In contrast, *Dpp6* knockout produced no effect on ethanol drinking in either a binge-like or intermittent access procedure for both sexes, but did reduce nest quality and increased binge-like sucrose consumption. *Slc39a8* heterozygous knockout male mice showed a trend towards increased binge-like ethanol consumption, and mice of both sexes had significantly reduced immobility in a forced swim test. Taken together, these findings highlight the complexity of translating genetic findings between humans and model organisms, even for phenotypes that may appear to be similar across species (e.g. ethanol consumption), and confirm the importance of using a variety of phenotypes for comprehensive GWAS follow-up.

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Cocaine Preference in the Drosophila melanogaster Genetic Reference Panel

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Studies on the genetic basis of susceptibility to cocaine addiction in human populations are challenging due to limited sample sizes, heterogeneity of genetic backgrounds, and environmental variability. *Drosophila* present a powerful model system for investigation into the genetic underpinnings of cocaine addiction, using preference for cocaine as a proxy for addiction behavior. Utilizing the Microplate Feeder Assay (MFA), we quantified cocaine preference for over 80,000 flies across 450+ distinct genetic backgrounds of the *Drosophila melanogaster* Genetic Reference Panel (DGRP). We provided individual flies with a choice between a control food and food supplemented with 0.02% cocaine. The preference for each solution was quantified for each individual fly using a plate reader following a 22-hour exposure. We found significant, naturally occurring genetic variation for cocaine preference across these DGRP lines with significant sexual dimorphism, where male flies on average exhibit higher cocaine preference than female flies of the same line. Estimates of broad sense heritability of consumption were calculated using individual level data, as well as using DGRP line means, and were found to be ^{2} and ^{2} , respectively. Six genetic lines representative of both high cocaine preference and mean cocaine preference were selected for single-nuclei multiomics investigation. These data will facilitate future genome-wide association analyses and describe the transcriptomic and conformational changes specific to specific cocaine preference predispositions. Our observations that innate cocaine preference is dependent on genetic background and sex will likely also apply to genetic risk susceptibility for cocaine addiction in human populations.

Identification of gene variants underlying C57BL/6 substrain differences in stroke vulnerability.

Megan Mulligan
Department of Genetics, Genomics and Informatics, UTHSC

MK Mulligan[1], L Zhao[2], V Kumar[3], TS Nowak Jr[2]

Human epidemiological and GWAS studies have identified non-genetic (e.g., smoking, diabetes, obesity) and genetic risk factors associated with stroke. However, genetic impacts on the severity of stroke injury once it occurs are largely unknown. Panels of inbred mice segregating millions of variants have been used to identify a number of vulnerability genes. We extend these studies by evaluating differences in infarct volume among genetically similar C57BL/6 (B6) inbred mouse substrains following permanent tandem occlusion of the middle cerebral artery and ipsilateral common carotid arteries. Infarcts are significantly ($p < 0.05$) smaller in J and ByJ substrains originating prior to 1962 compared to N substrains derived after 1974. This suggests that mutations increasing vulnerability became fixed in the N lineage between these times. Differences are heritable in F1 hybrids generated by crossing less vulnerable J or ByJ and more vulnerable NJ or NCrl substrains. Progeny resemble the vulnerable parent indicating a dominant mode of inheritance. We use QTL mapping in separate cohorts of F2 mice derived by crossing J with NJ (n=311) or ByJ with NCrl (n=96), as well as CRISPR-Cas9 genetically engineered mice, to identify genes involved in stroke vulnerability. These approaches converge on a missense mutation in *C*yfip2 (S968F) on chromosome 11 as a major source of substrain variation in acute stroke vulnerability. Additional loci on chromosomes 7 (6.7–77 Mbps) and X (14.6–132 Mbps) have complex genotype x parent of origin effects, potentially underlying the sex differences (female < male) seen in J and ByJ substrains.

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Joint analysis of multiple trio genomic datasets for the discovery of novel dominant epilepsy genes

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Background/Objectives: The epileptic encephalopathies (EEs) and epilepsy with co-morbid intellectual disability (ID) are groups of epilepsy characterized by refractory seizures and developmental regression. Both groups have been shown to have underlying monogenic causes. However, despite state-of-the-art testing, a significant proportion of people with these types of epilepsy do not receive a molecular diagnosis, suggesting yet-to-be-identified genetic causes. Our objective was to identify novel epilepsy with ID and EE genes through joint analysis of multiple trio genomic datasets.

Methods: We assembled WGS or WES datasets with associated EE or epilepsy with ID HPO terms. Datasets were from the FutureNeuro Research Centre (148 trios, 9 quads), the Epilepsy Genetics Initiative (29 trios), Epi4K/EPGP (337 trios), Undiagnosed Diseases Network (9 trios,1 quad), CSER (21 trios, 1 quad) and the UK 100,000 Genomes Project (269 trios). A GATK4.2.0 pipeline was used for variant calling. A statistical model using denovolyzeR was utilized to identify genes with a significant excess of DNVs.

Results: A total of 814 trios and 11 quads were included in the final analysis. We identified 13 genes with a significant excess of DNVs, of which 11 were established monogenic causes of epilepsy. Among the potentially novel genes, predicted damaging *MAST4* variants were observed in three unrelated patients. All *MAST4* patients had epilepsy and a similar developmental phenotype.

Conclusion: Combining genetic and phenotypic data, we report the significant enrichment of DNVs across over 2,000 individuals who underwent WES/WGS. We implicate de novo variants in *MAST4* as a cause of epilepsy with ID.

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Hypothalamic PACAP regulates both depression and fatigue: An optogenetic investigation following a transcriptomic analysis of the strain-dependent drug treatment effect on a co-susceptibility mouse model

Gang Chen

Jinan University

Hailou Zhang1,2, Gang Chen1,2*

Depression, characterized by core symptoms such as low mood, is also frequently presented with fatigue. Individuals with either fatigue or depression have an approximated two-fold higher risk for the comorbid presentation of both traits. A clinic study has shown that depression and fatigue shared a partial genetic predisposition. However, the mechanism of the comorbidity remains largely unknown. Here we developed the genetic models that showed differential co-susceptibility of depression and fatigue following chronic stress in two strains. We then used drugs that are known to treat depression or fatigue to validate the model. Finally, we performed the transcriptomic sequence analysis of the hypothalamus, pivotal for both depression and fatigue. We found that following chronic unpredictable mild stress, Balb/c mice showed both depression and fatigue: a Qi-tonifying Chinese medicine Sijunzi Decotion (SJZ) alleviated both symptoms, whereas a heat/fire-clearing medicine Yueju Pill (YJ) only alleviated depression. In contrast, 129S1/sv mice only showed depression, which was alleviated by YJ, but not SJZ. Based on the signaling pathway analysis of transcriptome, the neuropeptide PACAP and a few genes in the NF-kappa B signaling pathway in the hypothalamus may participate in both depression and fatigue. We confirmed the role of PACAP by showing both depression and fatigue behaviors following an optogenetic inhibition of the PACAP-ergic neurons in paraventricular nucleus of hypothalamus (PVH) in the PACAP knock-in mice. Together, we established a model for co-susceptibility of depression and fatigue symptoms, and PACAP in the PVH is the first demonstrated to regulate both of them.

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Outstanding Travel Awardees

Time: Thursday, 25/May/2023: 2:45pm · *Location:* Large Lecture Theatre in HBB (11 on campus map)
Session Chair: Helen Kamens

Elucidating the cellular basis of dopamine and oxytocin interactions underlying pair bonding

Meredith Loth
University of Colorado Boulder

Meredith K. Loth[1], Julia C. Schmidt1, Cassandra A. Gonzalez1, David S.W. Protter1, Zoe R. Donaldson[1,2]

The life-long pair bonds formed by monogamous prairie voles require concurrent dopaminergic D2 receptor and oxytocin receptor activation in the nucleus accumbens. However, it remains unclear whether concurrent signaling is occurring at the same or different cells. We used multiplex in situ hybridization to map the cellular distribution of prairie vole dopamine D1 receptor (*Drd1*), dopamine D2 receptor (*Drd2*), and oxytocin receptor (*Oxtr*) mRNA in the nucleus accumbens of sexually naïve and pair bonded prairie voles. We found that *Oxtr* is widely expressed across *Drd1*+ and *Drd2*+ cells. We next examined whether pair bond formation led to changes in cellular distribution of *Oxtr* transcripts. We observed a significant increase in co-expression of *Oxtr* and *Drd1/2* transcripts as a function of pair bonding, suggesting that mating may not unilaterally increase abundance of any one transcript, but rather affects their co-expression in a subset of cells. We performed a parallel experiment in promiscuous meadow voles, where mating and cohabitation do not lead to bond formation. We did not observe an increase in co-labeled cells in this species, suggesting that the changes observed in prairie voles reflect bond status rather than the experience of mating and cohabitation *per se*. Together, these results suggest that the required concurrent activation of oxytocin and dopamine d2 receptors during bond formation may lead to integration of neuromodulatory signaling at the cellular level rather than distinct cell types and that bonding reshapes the potential convergence of these signaling pathways in a subset of cells.

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Cell Adhesion Molecule 2 and cannabinoids: A point of physiological and behavioural drug use vulnerability

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Genome-wide association studies identify *Cell Adhesion Molecule 2* (*CADM2*) as a candidate risk gene for lifetime cannabis use and posit its involvement in neurobiological processes that overlap with cannabinoid activity. However, *CADM2* polymorphisms also associate with personality traits that are risk factors for substance use, thus obscuring the verity of its role in cannabis use. We therefore assessed the role of *Cadm2* in behavioral, physiological, and neurobiological features relevant to cannabis vulnerability using a knockout (KO) mouse. Preference for Δ9-tetrahydrocannabinol (THC) and cannabis oil containing edibles was lower in KO mice compared to littermates. THC also induced hyperlocomotion instead of expected hypolocomotion in KO mice, though there was no evidence of drug metabolism differences based on plasma levels of THC and its metabolite 11-hydroxy-THC. While KO mice showed an attentional deficit and resilience to impulsivity under drug-free conditions, THC challenge did not impact 5-choice serial reaction time task performance in KO mice. We further investigated the electrophysiological properties of prelimbic layer 5 principal neurons via whole-cell patch clamp recording and found membrane resistance was significantly greater in KO mice compared to WT. However, we report no differences in the expression of ionotropic glutamate and GABA receptor subunits that were previously correlated with *CADM2* expression, indicating that functional differences are not consequent of abnormal expression of these receptors in the frontal cortex. In conclusion, we demonstrate that *Cadm2* mediates response to cannabinoids from behavior to physiology, providing credibility to human findings that suggest *CADM2* variation directly affects cannabis use liability.

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Alcohol-Induced Alternative Splicing of Dopamine-2 Receptors in Drosophila Memory Circuits

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Repeated alcohol experiences produce long-lasting memories for sensory cues associated with intoxication. These memories can problematically trigger relapse in individuals recovering from alcohol use disorder (AUD). However, the molecular mechanisms underlying these memories have yet to be fully understood. We have recently demonstrated that formation of ethanol-associated memories disrupts alternative splicing of Dop2R in memory-encoding neurons in Drosophila melanogaster. These memory-encoding mushroom body (MB) neurons are required for Drosophila to make associative memories like ethanol-associated memories. Knocking down Dop2R or genes required for alternative splicing in MB neurons reduces ethanol-memory formation. This suggests that alternative splicing of Dop2R may be required for alcohol preference and memory formation. In order to understand the functional consequences of Dop2R alternative splicing, we generated mutant Drosophila that have forced expression of the naive or trained isoform of Dop2R. Using a novel two choice assay, we assessed mutant preference for an odor that was associated with intoxicating doses of ethanol following Pavlovian conditioning. We found that splicing of Dop2R impacts the dynamics of choice behavior and preference for ethanol. We also assessed mutant behavior in an operant self-administration assay and found that mutants expressing the trained isoform also had higher rates of self-administration. From this we conclude that alcohol-induced alternative splicing of Dop2R in memory circuits has functional consequences. These findings contribute to the growing body of literature that elucidate the role of dynamic splicing in the nervous system, and directly implicate alternative splicing in the development of AUD.

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Transcriptional signatures of social-stress escalated alcohol consumption

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LSU Health Sciences Center

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Social stress is a critical risk factor for many psychiatric illnesses including addiction. Individuals that consume alcohol to alleviate negative social situations are more likely to be diagnosed with an alcohol use disorder. However, the precise neural mechanisms underlying social stress-escalated alcohol consumption are not well understood. Using a system for activity-dependent genetic labeling and a mouse model for social defeat stress (SDS)-induced escalation of alcohol consumption, we examined the overlap between neurons activated by SDS and alcohol consumption within the same animal. We used the bigenic *Fos-2A-Cre:Ai14* mice in which the expression of an estrogen receptor-fused inducible Cre-recombinase is driven from the Fos promoter along with Cre-dependent reporter tdTomato (*Ai14*). We found that repeated SDS increased alcohol consumption in male and female mice and led to robust neural activation in several brain regions. Of these, the paraventricular thalamus (PVT) was particularly intriguing. The PVT is at the interface of neural systems that mediate arousal and motivated behaviors. Intriguingly, the PVT was also strongly activated by alcohol exposure and we found a robust overlap (88%) between cells activated by SDS and those activated by alcohol. A majority of the SDS-activated cells in the PVT expressed kappa and mu opioid receptors and projected to the zona incerta, nucleus accumbens, basolateral, and central amygdala. Finally, chemogenetic inhibition of SDS-activated cells in the PVT attenuated stress-escalated alcohol consumption. Experiments are currently underway to transcriptionally profile activated cells at single cell resolution to determine celltype specific neuroadaptations caused by SDS, alcohol, and both.

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