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15th Canadian Neuroscience Meeting
Abstract Proceedings

Abstracts

15th Canadian Neuroscience Meeting
May 12- 15, 2022, Toronto, Canada

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Dear Colleagues and Friends,

We are very happy to welcome you back in person for the 15th annual Canadian Neuroscience Meeting in Toronto. The CAN meeting chair, **Alyson Fournier**, and co-chair **Ian Winship** worked hard over the last months to put together an innovative meeting program, and we are very excited to welcome you to Toronto.

Highlights of this year's scientific meeting include invited speakers **Gordon Fishell, Valina Dawson, Mark Nelson, Frank Bradke, Margaret McCarthy** and Brain Prize winner **Elisabeth Tournier-Lasserve**. Plenary and parallel symposia, proposed by our members complete our diverse scientific program.

The 2022 Advocacy lunch session, chaired and organized by CAN advocacy committee chair **Karun Singh**, will feature a special training session with **Wai Haung (Ho) Yu**, who has extensive experience in international science advocacy, and notably with SfN.

We are also excited to host a panel discussion about the film **Picture a Scientist** in the Equity Diversity and Inclusion session, organized by EDI committee chair **Jibran Khokhar**.

A special highlight of our meeting will be the lectures by award-winning young neuroscientists. We are pleased to host the CAN 2022 New Investigator Award winner **Boris Bernhardt**. Highlights will also include presentation by the top three winners of the CAN-CIHR-INMHA Brain Star Award winners, **Archana Gengatharan**, **Yash Patel** and **Xuming Yin**.

Independently organized satellite symposia complement and complete this exciting program, check them out here: https://can-acn.org/meeting-2022/2022-satellite-meetings/

Some of the most engaging sessions are always the poster sessions featuring the work of our trainees, so we really look forward to meeting and chatting with poster presenters.

We hope you enjoy this program and look forward to welcoming you.

Shernaz Bamji

President of the Canadian Association for Neuroscience

May 12 – 15, 2022

Toronto

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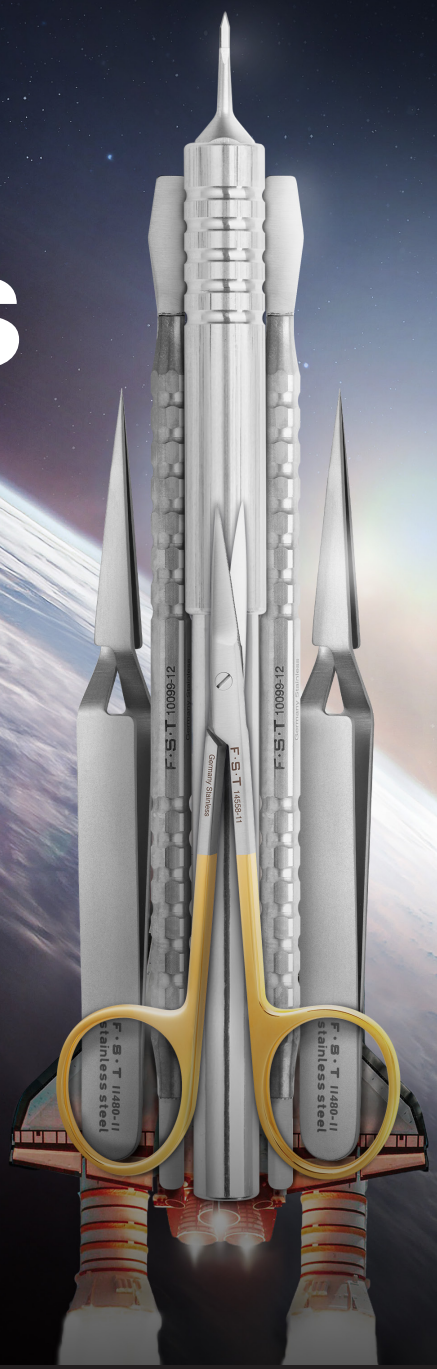

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WE'RE ALL DIFFERENT AND THAT'S WHY THIS IS SO IMPORTANT.

Women are twice as likely to suffer from depression, dementia and stroke as we age. Yet most brain research hasn't studied the links between sex, gender and disease. It's time for new, more equitable perspectives. That's why Women's Brain Health Initiative is teaming up with Brain Canada to provide grants that help close the research gap.

All the art above was generously donated in support of this important cause. Our thanks to them. Should you want to contact or follow them on Instagram: 1. @DorisRoseArt 2. @SeanaDraws 3. @SoxBoots 4. @Gholme. 5. @HowardAlstad 6. @Andy.Berlin 7. @JamesMcMullanArt 8. @SeanaDraws 9. @Daisy_Patton 10. @GeoffreyDraws 11. @JasonBoydKinsella 12. @Ewa_Look 13. @WinifredOffTheMat 14. @Jessica_A_McVicker_Art 15. @Chem.Laura 16. @Gholme

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Keynote and Plenary Talks:

Presidential Lecture: Making up your mind: the intimate dependence and remarkable precision of cortical interneurons - Gordon Fishell, Harvard Medical School

Classic work from two decades ago demonstrated that inhibition is mediated through an array of over 50 discrete cortical cell types. Each of these possess unique shapes and properties, suggesting that they have specific roles in the brain. Despite this, our understanding of how such inhibitory neuron diversity is generated and assembled into functional cortical circuits is lacking. Parvalbumin and somatostatin interneurons, the two largest populations of inhibitory cortical cells are generated in a specialized region of the subcortex, known as the medial ganglionic eminence. Amazingly, both these cell types migrate during development across the brain to form canonical circuits with excitatory cortical cells. By studying their gene expression during their incorporation into cortical circuitry, we have discovered key regulators of their development, which provided us with the tools to interrogate the different subtypes and witness and perturb their development. These advances provided the tool kit to start tackling two big questions. How do these cells find their right excitatory cell partners in the brain and just how selective are these connections? In this talk, I will focus on the somatostatin

populations, which we have recently found selectively connect to different excitatory populations, with one type targeting corticofugal cells and the other targeting intercortical relay neurons. Moreover, it seems these relationships depend on excitatory cells providing signals to the interneurons when they arrive in the cortex. The output and relay excitatory cells, which reside in different layers, appear to provide "instructions" to somatostatin cells as they settle within the cortex, allowing them to literally "learn on the job". This indicates the existence of a lock and key specificity in connectivity that we are only beginning to understand.

Featured Plenary Speaker 1: Decoding Parkinson's disease - Valina Dawson, John Hopkins

Institute of Institute for Cell Engineering, Departments of Neurology, Neuroscience and Physiology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

Parkinson's disease is characterized by the pathologic accumulation of misfolded α-synuclein protein leading to intracellular inclusions (Lewy bodies and Lewy neurites). PD presents with both motor and non-motor symptoms, with the motor symptoms largely due to the loss connectivity within the motor circuit of dopamine neurotransmission from the substantia nigra par compacta leading to a rest tremor, slowness of movement, rigidity, and postural instability. The non-motor symptoms of anxiety, depression, sleep disorders, autonomic dysfunction, constipation, and cognitive impairment are related to pathologic α-synuclein affecting other peripheral neurons and brain circuits. Ultimately the devastating symptoms of Parkinson's disease are due to loss of functional connectivity and neuronal cell death. The pathophysiology of Parkinson's disease is complex involving mitochondrial dysfunction, disruption of cell signaling, neuronal cell death and neuroinflammation. We will discuss how pathologic misfolded α-synuclein activates and promotes pathogenic cellular processes and how identification of critical molecular pathways can reveal promising therapeutic interventions that could be that could be leveraged into disease-modifying therapies to prevent or slow neurodegeneration in Parkinson's disease.

Brain Prize Lecture: From CADASIL to other cerebral small vessel diseases. How genetics can inform pathophysiological pathways - Elisabeth Tournier-Lasserve, Université Paris Diderot

Sponsored by the Lundbeck Foundation

Cerebral Small Vessel Disease (CSVD) is a leading cause of ischaemic and hemorrhagic stroke, and dementia. CSVD is caused by various pathological processes affecting cerebral small penetrating arteries, capillaries and/or venules. Two major risk factors, hypertension, and age, underpin most

cases. However, the molecular pathways leading to small brain vessels lesions in common CSVD are still largely unknown. In addition to common CSVD, several rare monogenic CSVD have been identified in the last 25 years. The most frequent of them is CADASIL, an autosomal dominant condition caused by highly stereotyped mutations in NOTCH3. The identification of this gene, of the clinical phenotype and cellular/molecular basis of CADASIL was a breakthrough in the CSVD field, opening an avenue to decipher CSVD mechanisms. Later, the tremendous progress of molecular approaches allowed the identification of the genes involved in several additional monogenic CSVD, including HTRA1, COL4A1/COL4A2, CTSA, LAMB1, KCNA5 related CSVD. This continuously expanding group is highly heterogeneous both on a clinical and genetic point of view. There is also a great diversity in the proteins encoded by "CSVD" genes. However, several of these genes encode either extra cellular matrix structural proteins or proteins expressed in the vascular matrisome. In addition, various up- or down- regulating classes of mutations within a given matrisome gene lead to distinct CSVD. Interestingly, variants of some of these genes have been strongly associated with common CSVD. Altogether these data opened avenues to decipher CSVD mechanistic pathways. However, screening of all known CSVD genes in 2022 does not identify a causative mutation in familial cases. Novel network-based computational and statistical approaches using genome-wide data from unrelated CSVD patients are currently used to find the missing genes

Featured Plenary Speaker 2: Rescuing cerebral blood flow deficits in small vessel disease - Mark Nelson, University of Vermont

Cerebral small vessel diseases (SVDs) are a central link between stroke and dementia—two comorbidities without specific treatments. Despite the emerging consensus that SVDs are initiated in the endothelium, the early mechanisms remain largely unknown. Deficits in on-demand delivery of blood to active brain regions (functional hyperemia) are early manifestations of the underlying pathogenesis. The capillary endothelial cell strong inward-rectifier K+ channel Kir2.1, which senses neuronal activity and initiates a propagating electrical signal that dilates upstream arterioles, is a cornerstone of functional hyperemia. Here, using a genetic SVD mouse model, we show that impaired functional hyperemia is caused by diminished Kir2.1 channel activity. We link Kir2.1 deactivation to depletion of phosphatidylinositol 4,5-bisphosphate (PIP2), a membrane phospholipid essential for Kir2.1 activity. Similar results were obtained using an Alzheimer's disease (5xFAD) mouse model (Mughal, Function, 2021) Systemic injection of soluble PIP2 rapidly restored functional hyperemia in SVD mice, suggesting a possible strategy for rescuing functional hyperemia in brain disorders in which blood flow is disturbed (Dabertrand, PNAS, 2021).

Keynote Lecture: Mechanisms of Axon Growth and Regeneration - Frank Bradke, German Center for neurodegenerative diseases

Sponsored by SickKids Neurosciences & Mental Health Research Program AND the SickKids Garry Hurvitz Centre for Brain & Mental Health

In this lecture, Frank Bradke will discuss his research on how neurons initially polarize to generate and extend their axon. He will then show how his group exploits the underlying developmental mechanisms to elicit axon regeneration in the adult after a spinal cord injury.

Almost everybody who has seen neurons under a microscope for the first time is fascinated by their beauty and their complex shape. Early on during development, however, neurons look round and simple without signs of their future complexity. How do neurons develop their sophisticated structure? How do they initially generate domains that later have distinct functions within neuronal circuits, such as the axon? And can a better understanding of the underlying developmental mechanisms help us in pathological conditions, such as a spinal cord injury, to induce axons to regenerate?

Here, I will talk about the cytoskeleton as a driving force for initial neuronal polarization and axon growth. I will then explore how cytoskeletal changes help to reactivate the growth program of injured CNS axons to elicit axon regeneration after a spinal cord injury. Finally, I will discuss whether axon growth and synapse formation could represent mutually excluding processes. Following this developmental hypothesis helps us to generate a novel perspective on regeneration failure in the adult CNS and to envisage new paths to overcome it. Thus, this talk will describe how we can exploit developmental mechanisms to induce axon regeneration in the adult after a spinal cord injury.

Featured Plenary Speaker 3: Surprising Origins of Sex Differences in the Brain -Margaret McCarthy, University of Maryland

It's not easy being male. Male fetuses die at a higher rate, are more likely to be born prematurely, more likely to suffer a birth injury, and if they do will fare far worse than females. Postnatally boys are diagnosed with autism spectrum disorders more often than girls, have on average more severe and earlier onset schizophrenia, experience markedly higher rates of attention and hyperactivity disorders and are three times as likely to have language and learning disabilities. This marked gender bias so early in life compels us to understand the biological origins of sex differences in the brain. Animal models free of the complicating influences of gender bias offer the best hope for identifying cellular and molecular mechanisms by which sex differences are established and maintained.

Sex differences abound throughout the brain and range from the macro-, size of entire regions, to the micro-, the average density of synapses along a dendrite, to the mini-, transcriptomic profiles.

Androgens derived from the fetal testis drive the sex differentiation process, resulting in a masculinized brain phenotype that will endure across the lifespan. Identifying the mechanisms of androgen mediated masculinization of the brain has been a long-standing goal with recent advances highlighting surprising roles for inflammatory signaling molecules and immune cells. Moreover, membrane derived signaling molecules such as endocannabinoids and prostaglandins play central roles in modulating the behavior of non-neuronal cells such as microglia. Exposure to exogenous substances that intersect with these systems, including cannabis and NSAIDs, can derail normal developmental trajectories if exposure occurs during a critical window. Lastly, inflammation during pregnancy is a major risk factor for development of neuropsychiatric and neurological disorders in the offspring. In this talk recent findings on how the immune system sculpts enduring sex differences in the healthy brain will be reviewed and the implications for disease risk discussed.

New Investigator Award: Boris Bernhardt, McGill University

Sponsored by Neuroscience and Mental Health Institute (University of Alberta)

Charting human brain organization and development across multiple scales

Boris Bernhardt, PhD
Assistant Professor of Neurology and Neurosurgery
Canada Research Chair in Cognitive Neuroinformatics

My talk will outline some of our lab's recent research and methods development to study the spatial organization of human brain microstructure, function, and connectivity. I will also overview how these approaches can be used to better understand typical as well as atypical human brain development.

Plenary symposia

Plenary symposium 1: Mitochondrial function and dysfunction in Parkinson's disease: insights from native and model cells

Mechanisms of metabolic dysfunction in synucleinopathies - Scott Ryan, University of Guelph

Neuronal loss in Parkinson's Disease (PD) is associated with aberrant energy homeostasis and impaired proteostasis in dopaminergic (DA) neurons. Linking these two pathologies is a major hurdle in developing new therapies for PD. It has been proposed that the interaction of α-syn with anionic membranes is critical for neurotransmitter release and vesicle recycling. We thus asked whether a pathophysiological connection between dopamine transmission, metabolic dysfunction and proteostasis exists in PD that centers on the ability of α-syn to interact with mitochondrial and/or synaptic membranes. We utilized a patient-derived human pluripotent stem cell model (hPSC) of PD that allows for comparison of A53T-SNCA mutant neurons against isogenic mutation-corrected controls. Following a floor plate-derived differentiation paradigm to DA neurons, we determined that A53T neurons have decreased levels of dopamine coupled to increased levels of oxidized dopamine in the form of DA-protein adducts leading to increased mitochondrial and proteostatic stress. Using an unbiased □-syn-interactome approach we found that in control neurons, α-syn interacts with enzymes important for flux through the pentose phosphate pathway and that this interaction occurs on synaptic vesicles. Moreover, we found that this interaction is lost in the context of A53T-SNCA mutant neurons resulting in a depletion of NADPH and subsequent depletion of glutathione (GSH), a major antioxidant that scavenges DA-radicals. N-acetyl cysteine (NAC) is GSH precursor that is clinically approved and has recently shown benefits in clinical trials against PD. We show that NAC might offer therapeutic benefit in synucleinopathy with respect to normalizing DA levels by increase GSH synthesis. In addition to informing on the mechanism of α-syn mediated toxicity, our data offer insight into protective mechanisms that may offer therapeutic benefit.

Mitochondrial dysfunction in idiopathic Parkinson's disease, what can patient-derived induced neurons tell us? Janelle Drouin-Ouellet, Université de Montréal

90% of Parkinson's disease (PD) cases are idiopathic. Although highly heterogenous in their clinical presentation, idiopathic PD cases share a single most important risk factor, which is age. The stem cell-based patient-derived models of PD currently available do not maintain the aging signature at a molecular level, hindering our understanding of this specific aspect of idiopathic PD pathophysiology as these cases are not caused by monogenic mutations and usually develop later in life as compared to familial cases. Recently, we developed a method allowing the direct conversion of skin fibroblasts of PD patients to induced dopaminergic neurons (iDANs), the neuronal type the most affected in PD. Directly reprogrammed neurons maintain critical aspects of the age signature of the donor, including age-related changes in the transcriptome, the reactive oxygen species (ROS) levels, DNA damage, autophagy impairment and mitochondrial dysfunction. As these cellular changes are suspected to play crucial roles in the development of idiopathic PD, we use this model to explore pathophenotypes related to mitochondrial dysfunction in PD patient-derived iDANs. This is done with the aim to provide a new system in which molecular-based stratification of the idiopathic PD patient population can be achieved, with the long-term goal of refining patient selection for clinical trials and for the development of iDAN-based personalized medicine.

Mitochondrial dysfunction in dopamine neurons in Parkinson's disease: at the interface of cell-autonomous and non-cell autonomous mechanisms - Louis-Eric Trudeau, Université de Montréal

Although some of the key motor symptoms of Parkinson's disease are known to result from gradual age-related loss of dopamine neurons located in the substantia nigra, the root causes of this cell loss are still unclear. Multiple lines of evidence suggest that mitochondrial dysfunction can act as one of the triggers of this neurodegeneration. This presentation will examine the relationship between mitochondrial dysfunction and neuronal loss in Parkinson's disease from two different angles. First, evidence will be presented suggesting that the unique morphological and bioenergetic characteristics of nigral dopamine neurons makes them uniquely vulnerable to mitochondrial dysfunction in the context of a cell-autonomous pathological mechanism. Second, this link will be reexamined in the context of very recent work highlighting the possible implication of non-cell autonomous mechanisms initiated by disinhibition of immune responses in genetically susceptible mouse models of Parkinson's, leading to the attack of dopamine and other vulnerable neurons.

Plenary symposium 2: Neurovascular coupling in health and disease: what we know and what we need to know

Inter-pericyte tunneling nanotubes: at the heart of neurovascular dysfunction in optic neuropathies - Adriana Di Polo, Université de Montréal

Reduced blood flow and impaired neurovascular coupling are recognized features of glaucoma, the leading cause of irreversible blindness worldwide, but the mechanisms underlying these defects are unknown. Retinal pericytes regulate microcirculatory blood flow and coordinate neurovascular coupling through inter-pericyte tunneling nanotubes (IP-TNTs). Using two-photon microscope live imaging of the mouse retina, we found reduced capillary diameter and impaired blood flow at pericyte locations in eyes with high intraocular pressure, the most important risk factor to develop glaucoma. We show that IP-TNTs are structurally and functionally damaged by ocular hypertension, a response that disrupted light-evoked neurovascular coupling. Pericyte-specific inhibition of excessive Ca2+ influx rescued hemodynamic responses, protected IP-TNTs and neurovascular coupling, and enhanced retinal neuron function as well as survival in glaucomatous retinas. Our study identifies pericytes and IP-TNTs as potential therapeutic targets to counter ocular pressure-related microvascular deficits and provides preclinical proof of concept that strategies aimed to restore intrapericyte calcium homeostasis rescue autoregulatory blood flow and prevent neuronal dysfunction

Neurovascular coupling and functional connectivity in Alzheimer's disease mice: Effects of pharmacotherapy - Edith Hamel, McGill University

Alzheimer's disease (AD) is a multifactorial disease with cerebrovascular alterations detected before brain structural changes and clinical evidence of dementia. Brain imaging techniques using hemodynamic signals as proxy for neuronal activity during neurovascular coupling (NVC) and functional connectivity are increasingly used for detecting altered brain function related to cognitive deterioration. Using hemodynamic signals of whisker-evoked NVC and resting-state functional connectivity (Rsfc) measured longitudinally together with cognitive testing, we studied disease onset, progression, and response to therapy (simvastatin, SV) in a transgenic mouse model of AD (APP mice). APP mice displayed age-dependent NVC deficits and early alterations in Rsfc in regions associated with the sensory-motor and default-mode (DMN) networks. An increase in Rsfc strength within the DMN was first observed, which was followed by a decrease as disease evolved. SV restored NVC and cognitive decline, and prevented AD-specific alterations within the DMN. The findings, which show reversal of cognitive deficits and altered connectivity by early pharmacotherapy, will be discussed together with effects of a cerebrovascular pathology on both NVC and Rsfc.

Optical dissection of brain pericytes and capillary function during aging - Andy Shih, Seattle Children's Hospital

Deterioration of brain capillary flow and architecture is a hallmark of dementia. Clinical studies show marked loss of brain pericytes, but whether this is a cause or consequence of capillary defects remains unclear. We conducted cause-and-effect studies in mice by optically ablating pericytes in vivo. Focal pericyte loss in adult and aged mice caused capillary dilation without overt blood-brain barrier disruption. These abnormal dilations altered the distribution of blood cells at capillary junctions, and increased capillary flow heterogeneity in affected areas. Flow disturbance also caused capillary regression and enduring loss of vascular structure. In adult mice, pericyte contact and vascular tone could be restored within days through synergistic remodeling of neighboring pericytes. However, pericyte remodeling was slower in the aged brain, resulting in persistent capillary dilation. These findings establish a link between pericyte loss and disruption of capillary flow and structure. They also suggest that pericyte remodeling is a therapeutic target to preserve capillary function.

Plenary symposium 3: Cannabinoids and endocannabinoids in the context of neurological and psychiatric disorders

Synaptic dysfunction and altered plasticity in Huntington disease: Role of endocannabinoids - Lynn Raymond, University of British Columbia

Synaptic dysfunction underlies early sensorimotor and cognitive deficits and precedes neurodegeneration in a variety of disorders, including Alzheimer, Parkinson and Huntington disease (HD). A monogenic inherited disorder, HD manifests with cognitive, motor and mood disorders associated with progressive degeneration pf striatal spiny projection neurons and cortical pyramidal neurons. Cortico-basal ganglia-thalamic loops regulate movement selection and motor learning, which are impaired early in HD. Skilled motor learning is mediated in part by plasticity at cortico-striatal synapses, including endocannabinoid-mediated, high-frequency stimulation induced long-term depression (HFS-LTD). We found impaired HFS-LTD in pre-manifest HD mouse models, as a result of deficits in HFS-stimulated endocannabinoid synthesis. Inhibition of endocannabinoid degradation rescued HFS-LTD in brain slice recordings and improved skilled motor learning on a rotarod task. These results suggest novel targets for mitigating early symptoms of HD, And support the need for clinical trials to test the efficacy of modulating the endocannabinoid system in treatment of HD. Supported by the CIHR Fdn-143210 and Huntington Society of Canada

Endocannabinoids, Astrocytes and the Social Transmission of Stress - Jaideep Bains, University of Calgary

Survival requires organisms respond effectively to challenges or stressors. Exposure to stress also leaves a lasting imprint on the brain that may be important in fine-tuning future responses to stress. We have previously shown that stress, as well as the lasting imprint on key synapses in the brain, is transmitted, through social interactions, to others. How this occurs, is not known. Here we show that CB1Rs in the mitochondria of astrocytes in the olfactory bulb are a critical hub for guiding behaviors related to detection of negative affective states and the social transmission of stress.

Endocannabinoids, the Amygdala and the Regulation of Stress and Anxiety - Matthew Hill, University of Calgary

Endocannabinoids are well known to attenuate behavioral and neuroendocrine responses to stress, however the neural circuits through which they exert these effects have not been well established. Work from our lab has identified the amygdala as an important hub for endocannabinoids to modulate stress-related processes. Prompted by this, we have employed a combination of anatomical, chemogenetic and pharmacological approaches to establish amygdala circuits which regulate the stress response and how endocannabinoid signaling is integrated into these circuits. As endocannabinoid based drugs move forward for the treatment of stress-related psychiatric diseases, understanding the mechanisms by which endocannabinoids regulate these processes is essential.

Parallel symposia

Parallel Symposium 1: Novel Sources of neurogenesis in vivo and in response to neurological injury

PS1.1 *Direct neuronal reprogramming by temporal identity factors*

Camille Boudreau-Pinsonneault[1], Awais Javed[1], Michel Fries[1], Pierre Mattar[2], Michel Cayouette[1]

[1]Institut de recherches cliniques de Montreal, [2]Ottawa Health Research Institute

Temporal identity factors are sufficient to reprogram developmental competence of neural progenitors, but whether they can also reprogram the identity of fully differentiated cells is unknown. To address this question, we designed a conditional gene expression system combined with genetic lineage tracing that allows rapid screening of potential reprogramming factors in the mouse retina. Using this assay, we report that co-expression of the early temporal identity transcription factor Ikzf1, together with Ikzf4, another Ikaros family member, is sufficient to directly convert adult Müller glial cells into neuron-like cells, without inducing a proliferative progenitor state. Using genetic lineage tracing, histological, immunohistochemical and scRNA-seq analyses in vivo, we show that the reprogrammed cells arise from Müller glia and share morphological and transcriptional signatures with cone photoreceptors, as well as bipolar cells. Furthermore, we show that co-expression of Ikzf1 and Ikzf4 can reprogram mouse embryonic fibroblasts to induced neurons in culture by rapidly remodeling chromatin and promoting a neuronal gene expression program. This work uncovers general neuronal reprogramming properties for temporal identity factors in differentiated cells, opening new opportunities for cell therapy development.

PS1.2 *Recruiting quiescent neural stem cells in the injured spinal cord*

Catherine-Alexandra Grégoire[1], Jorge Barreto[2], Olivier Tastet, Louis-Charles Levros, Loic Cochard, Brianna Goldenstein, Sandra Joppé, Anne Aumont[3], Steve Lacroix[4], Karl Fernandes[3]

[1]Université de Montréal, [2]Université Laval, [3]Université de Sherbrooke, [4]CHUL

A central aim of adult stem cell research is to strengthen the regenerative responses of endogenous precursors. In the injured spinal cord, this goal is confounded by the heterogeneous and dynamic nature of the post-injury microenvironment. Here, we identify TGFB1 signaling as an endogenous, injury-induced suppressor of proliferation for ependymal cells, a central canal cell type having the properties of quiescent neural stem cells (NSCs). FoxJ1-expressing ependymal cells undergo complex spatiotemporal changes in proliferation after spinal cord injury (SCI), implying the presence of multiple

yet-unidentified regulators. RNA-sequencing of FoxJ1-expressing cells from the intact versus lesioned spinal cord revealed transcription factors and broad classes of transcriptional programs involved in the early responses of ependymal cells to injury. Upstream regulator analysis of these SCI-induced transcriptomic changes suggested a prominent regulatory role for several inflammatory regulators, including TGFB1. Direct administration of TGFB1 to spinal cord stem cells, both in vitro and in vivo, led to a loss of colony-forming ability, identifying TGFB1 is a potent negative regulator of spinal NSC proliferation. Consistent with this, pharmacological inhibition of TGFB1 signaling after contusion SCI restored proliferation in the central canal niche at the lesion epicentre, indicating that endogenous TGFB1 suppresses ependymal cell recruitment at the injury site. These findings provide insight into the regulatory mechanisms controlling ependymal cell responses to SCI and support the concept of targeting specific features of the post-injury microenvironment as a component of strategies to enhance NSC recruitment.

PS1.3 *Direct lineage reprogramming strategies for CNS repair*

Maryam Faiz[1]

[1]University of Toronto

BACKGROUND AND AIM: Direct lineage reprogramming (DLR) is an emerging technology for central nervous system (CNS) repair. DLR aims to replace cells lost to injury or disease by the conversion of other mature cells in the parenchyma. Neuronal loss is characteristic of many types of neurological disease and injury, and therefore DLR strategies aimed at restoring these cells are of significant clinical interest. While there have been many reports of astrocyte to neuron DLR, surprisingly few studies have focused on functional outcomes. With the goal of developing clinically relevant DLR therapies, here we examined the outcomes of astrocyte to neuron DLR in a preclinical model of stroke. METHODS: Ectopic expression of Neurod1, a transcription factor important for neuronal development, was used for DLR in the endothelin-1 mouse model of sensory motor stroke. Adeno associated delivery (AAV5) of Neurod1 and Cre-based cell tracking was used to monitor DLR and the types of neurons produced. In addition, behavioural tests for motor function were performed to assess functional outcomes and compared to rehabilitation (environmental enrichment), the gold standard for stroke therapy. RESULTS: Newly converted neurons (iNs) expressed pan-neuronal markers and expressed appropriate cortical neuron layer markers based on their anatomical position. Importantly, ectopic expression of Neurod1 led to an improvement in motor function, similar to what is seen with rehabilitation paradigms. CONCLUSIONS: We have demonstrated that ectopic expression of Neurod1 in astrocytes leads to functional improvement following stroke. These findings highlight the use of single factor DLR for CNS repair.

PS1.4 *Ischemic injury induces reprogramming and local neural regeneration in the adult brain*

Margarita Lui[1], Ayden Gouveia[1], Charvi Syal[1], Timal Kannangara[2], Jean-Claude Béïque[2], Diane Lagace[2], Baptiste Lacoste[1], Ling He[3], Fredric Wondisford[4], Jing Wang[1]

[1]Ottawa Hospital Research Institute, [2]University of Ottawa, [3]Johns Hopkins Medical School, [4]Rutgers-Robert Wood Johnson Medical School

Background: Direct in vivo cellular reprogramming has gained much attention for its therapeutic potential to replace lost neural cells in situ following stroke-related brain injury. To translate this new concept into clinical application, it is critical to develop pharmacological approaches that can enhance the in vivo cellular reprogramming process to generate sufficient numbers of mature neurons locally, thus improving the regenerative potential of the damaged brain. Here, we identified that ischemia-activated pericytes (a-pericytes) from the stroke infarct region can be reprogrammed into induced-neural precursors (i-NPCs) both in culture and in vivo, further producing induced-neurons (i-neurons). In addition, we showed that pharmacological approaches targeting a signaling-directed epigenetic pathway, an atypical protein kinase C (aPKC)-mediated Ser436 phosphorylation of CREB Binding Protein (CBP), can modulate the reprogramming/differentiation process. Methods: we used endothelin-1/L-NAME induced focal cortical stroke model, together with multiple tracing tools, to identify local i-NPCs derived from a-pericytes within the stroke lesion site. Results: Using NeuroTrace 500/525 dye (specifically labelling pericytes) and genetic lineage tracing mouse lines (Nestin-cre-ERT2/YFPflx, TBX18-cre-ERT2/YFPflx, NG2-cre-ERT2/YFPflx), we showed that a local population of Sox2+ i-NPCs within the lesion 3 days post-stroke was derived from a-pericytes (NeuroTrace 500/525 dye+, NG2-YFP+ or Tbx18-YFP+), but not from SVZ Nestin-YFP+ NPCs. In addition, we found that permanent deletion of the aPKC-CBP pathway using CBPS436A knock-in mice significantly increased the transient population of Sox2+ i-NPCs shortly after stroke but impaired vascular remodeling and perturbed motor recovery during the chronic phase of stroke. Intriguingly, we identified that compound C, an AMPK inhibitor, was able to facilitate reprogramming efficiency of a-pericytes into i-NPCs both in vivo and in vitro, reminiscent of CBPS436A mice's phenotype. We further demonstrated that sequential treatment of compound C and metformin in pericyte reprogramming culture can significantly enhance the i-neuron production from pericytes. Conclusion: These findings suggest that targeting the aPKC-CBP pathway to promote reprogramming/differentiation of pericytes into i-neurons is a potential therapeutic approach to regenerate the stroke-damaged brain.

Parallel Symposium 2: The amygdala and the response to reward cues

Sponsored by CERVO Brain Research Centre

PS2.1 *Acetylcholine dynamics in the BLA during reward learning*

Marina Picciotto[1], Richard Crouse[1]

[1]Yale University

The basolateral amygdala (BLA) is densely innervated by cholinergic fibers from the nucleus basalis of Meynert (NBM). It is increasingly clear that the BLA is important not only for behaviors related to fear learning, but also for learning cue-reward outcomes, and acetylcholine (ACh) has been shown to be important for BLA plasticity and multiple types of learning. We therefore used fiber photometry to measure real-time ACh release in the BLA using a GRABACh sensor as mice learned a cue-reward association in an operant task. We found that reward-related events initially were associated with a peak of ACh release that shifted toward the cue as animals learned the task. We then used an optogenetic strategy to stimulate ACh terminals in BLA and found that it improved cue-reward learning. Surprisingly, stimulation did not have to be contingent with the reward outcome to improve performance, suggesting that the ACh release was not signaling a reward prediction error. This study demonstrates that BLA ACh signaling is important for cue-reward learning, and suggests that ACh release induces plasticity in the structure that does not require release timed to a rewarding event.

PS2.2 *Approach behaviours and instrumental pursuit triggered by appetitive cues: role of the basolateral amygdala*

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BACKGROUND AND AIM: Environmental stimuli paired with rewards guide animals towards rewards essential for survival such as food, water and safety. These conditioned stimuli (CSs) direct behaviour in two major ways. First, they evoke approach responses, preparing animals to engage with imminent rewards. Second, CSs can become attractive themselves, such that animals will learn new instrumental actions simply to obtain them. Through these effects, cues exert control over psychology and behaviour, promoting reward-seeking actions when the reward is not immediately available. However, when CSs acquire too much control over behaviour, they can promote pathological reward pursuit, as in eating disorders or drug addiction. In a 1st experiment, we examined how the basolateral nucleus of the amygdala (BLA) modulates 1) CS-triggered conditioned approach responses, and 2) the ability of CSs to support the learning of a new instrumental action. In a 2nd experiment we examined how BLA projections to the nucleus accumbens (NAc) core contribute to these effects. METHODS: During Pavlovian conditioning sessions, water-restricted male rats learned to associate a light-tone cue (CS) with water (UCS) delivery into a dish. In Experiment 1 we determined how optogenetic stimulation of ChR2-expressing BLA neurons influences 1) CS-evoked approach

behaviors during Pavlovian conditioning and 2) the capacity of the CS to reinforce learning of a new instrumental action (lever pressing). In Experiment 2, we determined how stimulation of ChR2-expressing BLA→NAc core neurons influences these effects. RESULTS: In Experiment 1, during Pavlovian conditioning, pairing CS presentation with stimulation of BLA neurons potentiated CS-evoked water dish visits. This indicates enhanced conditioned approach and appetitive conditioning. During instrumental conditioning sessions, where rats could press a lever to obtain CS presentation (without water), pairing CS presentation with stimulation of BLA neurons also intensified responding for the CS. This suggests enhanced CS incentive value. In Experiment 2, pairing CS presentation with stimulation of BLA→NAc core neurons also potentiated CS-evoked water dish visits during Pavlovian conditioning, but it did not change instrumental responding for the CS. CONCLUSIONS: Increased activity in BLA neurons intensifies CS control over behavior, and this involves 2 dissociable mechanisms. First, by enhancing CS-UCS associative learning. This increases CS-triggered conditioned approach behaviors, preparing animals to engage with the forthcoming UCS. Second, by amplifying incentive motivation to pursue the CS. Furthermore, increased activity in BLA→NAc core neurons specifically is sufficient to promote Pavlovian approach behaviours, without effects on motivation to pursue the CS. The findings reveal new behavioural and psychological mechanisms through which the BLA and its projections mediate the response to reward-predictive cues.

PS2.3 *Optogenetic excitation of central amygdala amplifies 'wanting' but not 'liking' for sucrose reward*

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The central nucleus of amygdala (CeA) mediates both positively-valenced reward motivation as well as fear. BACKGROUND AND AIM: We have previously found that pairing reward delivery (either a sucrose pellet or intravenous cocaine reward) with optogenetic stimulations of central amygdala amplifies motivation for the paired reward at the expense of an alternative, unpaired reward. We further demonstrate that pairing CeA stimulation with touching an aversive shock rod paradoxically increases shock rod approaches and interactions. But does higher 'wanting' imply higher 'liking'? Evidence so far has been weak. METHODS: To test whether CeA stimulation enhances reward 'liking', we used the affective taste reactivity test, in which volume and rate of sweet or other tastes are controlled via intraoral cannula delivery into the mouth of rats. RESULTS: CeA ChR2 laser excitation failed to enhance positive hedonic orofacial reactions or 'liking' (e.g., tongue protrusions, paw licking) elicited by sucrose taste, despite enhancing 'wanting' in breakpoint measures and narrowly focusing motivation onto the laser-paired sucrose option in a 2-choice task. CeA ChR2 stimulation similarly failed to suppress negative 'disgust' reactions to bitter quinine (e.g., gapes, headshakes). CONCLUSIONS: Overall, these findings confirm that CeA ChR2 excitation selectively magnifies

incentive motivation and focuses 'wanting' narrowly on a laser-paired reward, without enhancing hedonic impact or 'liking' for the same sweet reward.

PS2.4 *Amygdala mechanisms distinguishing addiction vulnerability phenotypes*

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While not all individuals who try recreational drugs develop Substance Use Disorder (SUD), those that do are vulnerable to specific triggers that drive drug seeking even in the face of negative consequences. Preclinical evidence in rats suggests that sign- and goal-tracking individual differences predict differences in drug relapse vulnerability to discrete and contextual cues. These unique relapse vulnerabilities persist despite negative consequences of drug seeking actions. We focus on behavioral flexibility differences of sign- and goal-tracking rats, which are evident both before and after drug experience. We have established that discrete cue-triggered relapse vulnerable sign-tracking rats are less flexible than goal-tracking rats even before drug experience. While extended Pavlovian training promotes sign-trackers' ability to use state-dependent information to appropriately guide responding to cues, sign-trackers' persistent flexibility deficits relate to their inability to use cues to infer current outcome value based on prior experience. We've recently found basolateral amygdala (BLA) communication with the nucleus accumbens core (NAcC) prevents flexible behavior in sign-tracking rats. When we use chemogenetics to inhibit BLA-NAcC communication, sign-tracking rats show greater flexibility after outcome devaluation. The same manipulation has the opposite effect in goal-tracking rats that rely on BLA-NAcC communication to optimally express their flexible behavioral phenotype. We had originally hypothesized the flexibility of goal-trackers would be mediated by amygdala-cortical projections, and while we find a necessary role for find BLA-insular cortex (IC) communication in the expression of sign- and goal-tracking behaviors, this pathway does not support the behavioral flexibility of goal-tracking rats. In contrast, chemogenetic inactivation of BLA-IC also promotes flexibility in sign-tracking rats, similar to manipulations that disrupt amygdala-striatal communication. Together these results inform our understanding of the brain circuits driving sign- and goal-tracking differences before drug experience, which may aid in circuit investigation of sign- and goal-trackers' distinct relapse vulnerabilities observed after drug experience.

Parallel Symposium 3: The diverse roles of glia in stress and metabolic disorders

Sponsored by the BRaIN Program at the RI-MUHC

PS3.1 *Astroglial endozepines in the hypothalamic control of energy homeostasis*

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In the brain, the hypothalamus plays a key role in the control of appetite and body weight. This control relies on neuronal populations that sense circulating metabolic signals including lipids and activate neuroendocrine and behavioral responses to maintain body weight. Glial cells are now recognized for their key roles in brain energetics, neuronal activity and plasticity. Astrocytes, the most abundant glial cells, are implicated in complex and fundamental behaviours such as breathing and sleeping, and have recently emerged as key players in energy homeostasis. However, the mechanisms by which hypothalamic astrocytes affect energy balance neurocircuitry remain largely unknown. We identified Acyl-CoA Binding Protein (ACBP), also known as Diazepam Binding Inhibitor, as a protein strongly expressed in hypothalamic astrocytes where it regulates the intracellular metabolism of unsaturated fatty acids. ACBP is also secreted and cleaved to generate endozepines including the octadecaneuropeptide which modulate GABAA receptor signaling. We found that hypothalamic ACBP expression is regulated by the metabolic states in a circadian manner. Using targeted ACBP loss-of-function in GFAP astrocytes, we demonstrated that astroglial ACBP deficiency affected meal pattern and body weight without changing total calorie intake in ad libitum fed or refeeding conditions. ACBP KO in astrocytes promoted diet-induced hyperphagia and obesity in both male and female mice, an effect prevented by genetic rescue of ACBP in arcuate astrocytes. Interestingly, mice with astroglial ACBP deficiency were unresponsive to the anorectic effect of oleic acid. The ACBP-derived octadecaneuropeptide selectively activated anorectic/catabolic pro-opiomelanocortin neurons in the arcuate nucleus via a GABAa-independent mechanism and supressed feeding while increasing carbohydrate utilization via the melanocortin system, and induced weight loss in obese mice. These findings uncovered ACBP as a hypothalamic gliopeptide playing a key role in energy balance and exerting strong anorectic effects via the central melanocortin system.

PS3.2 *The role of astrocytes in stress-induced cognitive dysfunction*

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While stress is essential for survival and adaptation, intense or unrelenting stress particularly when experienced during development can have long-lasting negative effects. Indeed, stress experienced as a child has been shown to increase the susceptibility to anxiety and depression years later, as an adult. This is believed to be due to rewiring of neural circuits, heightening sensitivity to stress and increasing susceptibility to anxio-depressive disorders. While much has been studied regarding the effects of early-life stress on neurons, the contribution of non-neuronal cells which comprise over 50% of all brain cells remains poorly defined. To investigate the effects of early-life stress on astrocytes we

used a clinically translatable stress paradigm mimicking maternal neglect during a critical neurodevelopmental window. We show that early-life stress results in persistent modifications in memory as adults, specifically emotional memory. Early-life stress induced a persistent increase in blood glucocorticoids associated with profound changes in astrocyte structure and function into adulthood. Targeting glucocorticoid signalling on astrocytes, we were able to ameliorate the effects of stress on behaviour, underlining the importance of these cells in mediating the central effects of stress. Our data underscore the importance of studying astrocytes in the context of stress to identify new therapeutic targets to treat stress disorders.

PS3.3 *Role of the leptin receptor expressing pericyte in energy balance and beyond*

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Our lab recently discovered that a large portion of vessel-enwrapping hypothalamic pericytes express the leptin receptor (LepR) and that selective ablation of pericytic LepR leads to overeating and insensitivity of hypothalamic LepR neurons to circulating leptin. Importantly, we found that intravenously injected fluorescently tagged leptin was specifically retained at LepR pericytes and this retention was attenuated in mice that were deficient in pericytic LepR. Collectively, our data supports the view that LepR pericytes regulate blood vessel permeability in a leptin dependent manner. We now wish to delineate the precise mechanism of how LepR pericytes are engaged in creating localized leaks in the blood brain barrier to facilitate leptin access to hypothalamic LepR neurons and explore the consequences of hyperleptinemia on LepR pericyte function. Ultimately, we expect LepR pericyte to emerge as key link between obesity and certain comorbidities.

PS3.4 *Glia-Neuronal interaction in Health and Salt-Induced Hypertension*

Masha Prager-Khoutorsky[1]

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High dietary salt increases arterial pressure partly through activation of magnocellular neurosecretory cells that secrete antidiuretic and vasoconstrictor hormone vasopressin (VP) into the circulation. Here, we show that rats fed high dietary salt (7 days of salt-loading) develop local neuroinflammation in hypothalamic supraoptic and paraventricular nuclei harboring magnocellular VP neurons. Accumulation of activated microglia around VP neurons causes pruning of astrocytic processes, leading to decreased astrocytic coverage of VP neurons and impaired glutamate clearance by astrocytes. As a result, spillover of glutamate leads to the activation of extra-synaptic glutamate

receptors on VP neurons, contributing to enhanced activation of VP neurons, excessive VP secretion, increased arterial pressure and eventually hypertension.

Parallel Symposium 4: Neuronal dynamics underlying memory in the input and output structures of the hippocampus.

PS4.1 *Not just a compass: the role of the head-direction system in learning and memory during sleep*

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The head-direction (HD) signal is a crucial piece of information for navigation. It is processed by a population of HD neurons each coding for a specific direction of the head, the population of HD neurons thus being akin to a compass for the brain. This signal is conveyed from the anterodorsal nucleus (ADN) of the thalamus to the spatial navigation system in the entorhino-hippocampal region where spatial signals are represented, for example, by place and grid cells. During sleep, hippocampal place cells reactivate patterns that form with spatial learning, a phenomenon that is instrumental for memory consolidation. However, whether inputs to the hippocampus such as HD cells influence hippocampal activity during sleep remains unknown. Here, I will show that, during sleep, the HD cell population remains organized as during wakefulness in the ADN. In addition, the ADN-HD cell population reactivates coactivation patterns that form during recent spatial learning and this organized population activity influences downstream structures in the entorhino-hippocampal system. In conclusion, these findings shed light on subcortical processes at play for long-term memory formation.

PS4.2 *A cross-network oscillatory motif underpinning cocaine-paired memory retrieval*

David Dupret[1]

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Memories of drug experience invigorate behavioural actions biased towards drug-paired stimuli. These maladaptive memories engage many brain regions; however, the patterns of inter-region coordination that relate to cocaine-paired memory retrieval remain elusive. In this talk, I will be presenting ongoing work reporting a brain-distributed motif of cooperative network oscillations that underlies dynamic retrieval of cocaine-paired memory. By simultaneously recording oscillatory activity in the prefrontal cortex, nucleus accumbens, amygdala, hippocampus and ventral tegmental

area of the mouse brain, I will describe a higher-order, cross-network pattern of beta-band oscillatory activities that report initial recall of cocaine-paired memory, and its subsequent renewal following extinction. I will further discuss evidence that such beta-specific patterns of oscillatory coordination are organised by ventral tegmental area 4-Hz oscillations. Binding together a set of distributed brain networks in this manner may underlie the robustness of drug-paired memories, and hence the resilient nature of drug seeking behaviour.

PS4.3 *Prefrontal neuronal dynamics supporting memory integration and transformation*

Kaori Takehara-Nishiuchi[1]

[1]University of Toronto

BACKGROUND AND AIM: As memories become old, incidental details unique to each memory are mostly forgotten, whereas common latent patterns are retained. This process is thought to build generalizable knowledge of the external world, which allows for predicting adaptive behaviour in a similar new situation. Recent evidence in humans and rodents suggests that the integration and prediction processes critically depend on the medial prefrontal cortex (mPFC); however, how these processes are implemented in real-time neuronal ensemble dynamics remains unknown. METHODS: We recorded spiking activity in the prelimbic region of the mPFC while rats underwent context-dependent differential associative learning tasks. RESULTS: In the first study, the rats learned two distinct stimulus associations across several weeks. During this period, firing patterns of mPFC neurons became less selective for sensory features unique to each association while becoming more selective for their common relational feature. Notably, the patterns of increased relational coding followed time courses different from those of decreased sensory coding, implying that building abstraction is not merely a product of selective forgetting. We then conducted the second study to investigate the utility of the abstract, gist-like representations in the mPFC. Rats initially learned a "rule" that one of two neutral conditioned stimuli (CS1, 2) preceded eyelid shock in each of two rooms. On the test day, the divider between the two rooms was removed for the first time, allowing the rats to move between the rooms freely. When one of the CS was presented in a block, the rats successfully avoided the shock by moving to the room where the current CS had not been paired with the shock. This new goal-directed behaviour was not observed in other rats that did not learn the rule beforehand, suggesting that it arose from the transformation of the learned rule but not from the real-time acquisition of place aversion. Furthermore, immediately before the rats expressed the new goal-directed behaviour, mPFC neuron ensembles spontaneously reactivated the firing patterns associated with the learned rule. The timing of this spontaneous reactivation was tightly coupled with the initiation of the goal-directed behaviour. CONCLUSIONS: These findings suggest that the mPFC network possesses a unique coding property that allows extracting commonality across multiple experiences and transforming it to infer new adaptive behaviour.

Parallel Symposium 5: Alternative splicing in the health and disease of the mammalian brain

PS5.1 *Cell-specific epigenetic control of calcium ion channel splicing and function*

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BACKGROUND AND AIM: Voltage gated CaV2.2 channels are crucial gatekeepers between peripheral detection of noxious stimuli and central perception of pain. They are located at points of sensory detection in nociceptors and control transmission of noxious stimuli at nociceptor termini in the dorsal horn spinal cord. CaV2.2 channels are the targets of many drugs and neurotransmitters that activate G-protein coupled receptors to down regulate nociception. Nociceptors express a unique form of the CaV2.2 channel, through alternative splicing, which influences the sensitivity of CaV2.2 channels to inhibition by μ-opioid receptors. Our goal is to elucidate the mechanism of cell-specific alternative splicing of Cacna1b, the gene encoding CaV2.2 channels, exon 37a to allow the expression of a unique isoform of CaV2.2 in nociceptors that confers high sensitivity to morphine. METHODS: We investigate binding of CTCF to DNA using the electrophoretic mobility shift assay and chromatin inmunoprecipitation (ChIP) followed by qPCR. We use F11 cells and dorsal root ganglia (DRG) cells from the TRPV1tdTomato mouse strain, and quantify exon expression and DNA methylation by qPCR and bisulfite sequencing in nociceptors. RESULTS: We find that cell and exon-specific DNA hypomethylation permits CTCF binding, the master regulator of mammalian chromatin structure, which, in turn, controls splicing in the DRG-derived F11 cell line. We identify that CTCF binds Cacna1b exon 37a in several human and mouse cell lines. By electrophoretic mobility shift assay, we confirm that recombinant CTCF binds exon 37a, but not the neighboring homologous exon 37b. We have applied several methods to show that CTCF promotes Cacna1b exon 37a inclusion in Trpv1-lineage nociceptors during alternative splicing. In F11 cells, we show: 1) by ChIP-qPCR, that CTCF binds in exon 37a of Cacna1b in vivo, but not in exon 37b; 2) CTCF overexpression increases, and CTCF siRNA knockdown decreases exon 37a inclusion; 3) pharmacological inhibition of gDNA methylation, with 5-azacitine, increases exon 37a expression; and 4) CTCF siRNA knockdown occludes 5-azacitidine exon 37a increase. In mice, we show that DRG Trpv1-lineage nociceptors express exon 37a and have less methylation in locus 37a compared to DRG neurons that do not express Trpv1. Additionally, we find that following peripheral nerve injury exon 37a inclusion is reduced and methylation levels increased in comparison with sham controls. CONCLUSIONS: Our results show that hypomethylation of exon 37a, specifically in Trpv1-lineage nociceptors, likely permits CTCF binding and expression of CaV2.2

channel isoforms with increased opioid sensitivity in mice. Following nerve injury, exon methylation is increased and splicing is disrupted. Our studies define the molecular mechanisms of cell-specific alternative splicing of a functionally validated exon in normal and disease states and reveal a potential target for the treatment of chronic pain.

PS5.2 *Gain control of LTP and learning by alternative splicing of the GluN1 subunit of NMDA receptors*

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NMDA receptors are crucial ionotropic glutamate receptors playing key roles in developmental, physiological and pathological processes in the central nervous system. These receptors are heterotetramers comprised of two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits. GluN1 is encoded by a single gene, GRIN1, with 8 splice variants. Conventional wisdom is that GluN1 subunits do no more than bind glycine as a co-agonist with glutamate and are necessary for the proper assembly and surface delivery of the receptors. Although the splice variants were identified shortly after GRIN1 was discovered, the biological function of alternative splicing of GRIN1 remained unresolved. Recently, dysregulation of splicing of GRIN1 transcripts containing the alternatively spliced exon 5, which encodes a highly conserved 21-amino acid cassette (called N1 cassette), has been reported in individuals with autism spectrum disorder. To explore the function of splice variants of GluN1 in vivo, we generated mice lacking exon 5 (GluN1a mice) or constitutively expressing this exon (GluN1b mice). GluN1a and GluN1b mice are viable and develop normally. Ligand potency, magnesium block at -60 mV, Zn2+ inhibition and pH sensitivity were not different by genotype in cultured primary neurons from these mice. But, the presence of the N1 cassette did alter allosteric regulation. Namely, spermine increased NMDA evoked currents in GluN1a neurons whereas currents were reduced by spermine in GluN1b neurons. Similarly, 10 mM Mg2+ increased NMDA evoked currents at +60 mV in GluN1a neurons whereas Mg2+ reduced NMDA currents in GluN1b neurons. Using iPSC-derived neurons generated from an individual with autism spectrum disorder, we also observed increased Mg2+ potential of NMDA evoked currents which was consistent with the results from mouse neurons lacking the GluN1 N1 cassette. To explore the role of the N1 cassette in synaptic NMDA receptors, we recorded field excitatory postsynaptic potentials (fEPSPs) at Schaffer collateral - CA1 synapses using hippocampal slices from GluN1a and GluN1b mice. We found that fEPSP amplitude responses to increasing stimulation intensity, paired pulse ratio and NMDA:AMPA receptors ratios were all not different by genotype. However, long-term potentiation induced by theta burst stimulation was significantly lower in GluN1b slices. To assess if the N1 cassette might also affect NMDA receptor dependent learning and memory, we tested each genotype in the Morris water maze. GluN1a mice learned more quickly and had significantly better recall than did GluN1b mice. Unexpectedly, GluN1a mice performed better than wild type mice. Thus, our report answers a long-

standing question in neuroscience by demonstrating a biological function of alternative splicing of GRIN1. Funding from CIHR, Ontario Brain Institute and the Simons Foundation for Autism Research.

PS5.3 *Alternative splicing of AMPA receptor signalling complexes*

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[1]McGill University

BACKGROUND AND AIM: AMPA-type ionotropic glutamate receptors (AMPARs) are fundamental for fast excitatory neurotransmission across all brain regions. These cation-permeable channels consist of four pore-forming subunits, each of which can be alternatively spliced. Alternative splicing occurs in the ligand-binding domain (LBD) at a region called the 'flip/flop cassette', generating two splice variants: flip and flop. The expression pattern of flip and flop in the CNS is highly controlled, both spatially and temporally. Furthermore, flip and flop isoforms exhibit distinct pharmacological and kinetic properties and also differ in their responsiveness to allosteric modulators. Recent work from our lab has shown that alternative splicing of AMPARs unexpectedly dictates the intrinsic nanoscale mobility of the apo state. In the absence of agonist, flop receptors are inherently more mobile than flip receptors, which underlies differences in the time course of channel activation and sensitivity to allosteric regulation. In the brain, AMPARs do not act alone; they form signalling complexes with auxiliary proteins which modify their functional behaviour. Given this, we wondered whether AMPAR alternative splicing can also impact modulation by auxiliary subunits. METHODS: For recombinant experiments, we transiently co-expressed alternatively spliced AMPA receptor pore-forming subunits and auxiliary subunits in HEK293 cells. For native experiments, we prepared acute sagittal slices of mouse cerebellar vermis. We then performed electrophysiological recordings on excised membrane or nucleated patches using a fast perfusion system to measure channel gating properties. RESULTS: We find that one of the most prominent auxiliary subunits, transmembrane AMPAR regulatory protein gamma-2 (TARP γ2) is unable to regulate the time course of desensitization of flop receptors. In contrast, another important auxiliary subunit, Cornichon-3 (CNIH-3) is completely unaffected by alternative splicing. Our data suggest that this distinction can be explained by both structural and kinetic mechanisms. TARPs and CNIHs target different AMPAR gating modes, where TARPs act to slow desensitization via LBD interactions, while CNIHs primarily affect deactivation via the transmembrane region. Since alternative splicing also targets the AMPAR LBD to regulate desensitization, the flip/flop cassette dominates and acts as a master switch to selectively override TARP function. In addition, we show that other auxiliary protein families, namely GSG1L and CKAMP44, are unaffected by alternative splicing. Importantly, we extend our findings to the native system and demonstrate that the flip/flop cassette regulates fully- and partially-TARPed AMPARs in the cerebellum. CONCLUSIONS: Altogether, this work establishes that AMPA receptor alternative splicing is a complex regulatory mechanism that, in coordination with auxiliary subunit association, fine-tunes and diversifies synaptic transmission.

PS5.4 *A splicing code reveals an expanded landscape of brain microexons with direct genetic links to autism*

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BACKGROUND AND AIM: Alternative, neural 3-27 nt-long microexons have emerged as a critical regulatory hub in nervous system development and higher order cognitive functioning that is frequently disrupted in neurological disorders. Previously, neural microexons were largely detected using RNA-seq data from intact brain tissue. As such, microexons spliced in relatively rare cell types or weakly expressed genes may have been missed. Moreover, cis-elements important for microexon splicing have not been systematically defined, and whether these elements are directly disrupted by variants with causative roles in neurodevelopmental disorders has not been determined. METHODS: We have developed a machine learning model that reliably predicts neural microexons from input genomic sequence. We have combined this predictive code with MicroExonator, an RNA-Seq analysis tool for the de novo discovery and quantification of microexons. By performing in silico saturation mutagenesis, we have further used the code model to pinpoint sequences critical for splicing of known and novel microexons, as well as autism-associated variants that disrupt these elements. RESULTS: Applying MicroExonator to thousands of brain RNA-Seq datasets confirms more than 1,600 code-predicted novel microexons in human, most of which are detected in brain single cell RNA-Seq data. This expanded repertoire includes numerous examples that have neural cell type-specific splicing patterns, and many that elicit mRNA turnover and are controlled by previously unknown regulatory mechanisms. Applying the code to predict the impact of autism-linked variants compiled from the Simons Simplex Collection indicates that probands have a significantly higher burden of rare singleton microexon-associated variants than unaffected siblings. Remarkably, many proband-specific variants disrupt the splice sites of microexons, as well as critical RNA binding recognition motifs located distally from splice sites, both in autism-linked genes and genes not previously known to have causative roles in neurological disorders. CONCLUSIONS: Our results provide a greatly expanded atlas of brain microexons, demonstrate a direct impact of autism-associated genetic variation on this splicing program, and further uncover new genes and mechanisms linked to neurological disorders.

Parallel Symposium 6: Understanding dynamic neural circuit activity during defensive behavior with optical recording methods

Sponsored by CERVO Brain Research Centre

PS6.1 *Serotonergic modulation of ventral hippocampus underlies sex-related differences in anxiety*

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BACKGROUND AND AIM: Anxiety disorders disproportionately affect women, yet the neural substrates underlying sex-related differences in anxiety have been largely understudied. Our work focuses on the ventral hippocampus network and serotonergic neurons from the raphe nuclei, two key players in the modulation of anxiety levels. METHODS: Using retrograde viral vectors, we targeted the expression of fluorescent reporters, optogenetic tools or calcium sensors to the sub-population of serotonergic neurons that send monosynaptic projections to the ventral hippocampus. RESULTS: We show that selective optogenetic activation of ventral hippocampus-projecting serotonergic neurons increases anxiety levels in female, but not male mice. I will discuss the dynamics of serotonergic neuron activity in relation to aversive environment exploration, measured using fiber photometry. In addition, I will also present some of our recent results addressing the effects of serotonin on ventral hippocampus theta rhythm, a network state related to anxiety-like behavior. CONCLUSIONS: These studies highlight sexual dimorphism in the raphe-ventral hippocampus serotonergic pathway and provide novel insight about the neural circuits underlying increased vulnerability to anxiety in females.

PS6.2 *Sex differences in neural representation of threat in ventral hippocampal and prefrontal cortical projections to nucleus accumbens*

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BACKGROUND AND AIM: Although fear is essential for survival, excessive fear is implicated in a range of neuropsychiatric disorders. The nucleus accumbens (NAc) plays a role in learning about and behaviorally responding to appetitive and aversive stimuli by integrating input from several brain regions including the ventral hippocampus (vHIP) and prefrontal cortex (PFC). Here we investigate how neural activity in these projections is shaped by aversive experiences and how it guides defensive behavior in response to threat. METHODS: Using frame-projected independent fiber photometry (FIP) to image in vivo calcium activity in male and female mice, we recorded PFC and vHIP NAc-projecting neurons during a Pavlovian fear conditioning paradigm in which mice encountered both threat cues (CS+) predicting shock and neutral cues (CS-) with no outcome. RESULTS: Neural activity in both the vHIP-NAc and PFC-NAc encodes foot-shock and differentiates threat-predictive from neutral cues in a sex specific manner. Foot-shock increased activity in both pathways with response in PFC-NAc

augmented in females compared to males. These projections showed pathway and sex specific increases at cue onset with vHIP -NAc being elevated in males but not females and PFC-NAc being elevated in females but not males while both pathways exhibited suppression in anticipation of shock. Although both pathways respond to and discriminate threat predicting and neutral cues, neural representations did not predict freezing behavior. Consistent with this lack of relationship, pathway-specific chemogenetic inhibition did not impair cue-induced freezing. Given the role of the NAc in shaping motivated behavior, we examined if these NAc inputs might contribute to suppression of reward seeking by fear conditioned cues. Using a conditioned suppression paradigm in which aversive cues were presented while mice lever press for reward, we found that pathway-specific chemogenetic inhibition attenuated suppression of lever pressing by the CS+ in a sex-specific manner. CONCLUSIONS: Our findings suggest that both the vHIP and PFC convey information about threat prediction to the NAc medial shell to guide ongoing behavior with pathway-specific sex differences in neural encoding that may relate to sex differences in threat processing and risk for psychiatric disorders such as anxiety and depression.

PS6.3 *Synaptic transmission at the lateral habenula neural outputs in normal and pathological conditions*

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The lateral habenula (LHb) is an important part of the reward circuit as it provides 'negative value' signals: when an animal receives a reward that is less than expected (i.e. is disappointed) or anticipates punishment (i.e. expects something bad), the LHb is active. This information is thought to be used to shape future behavior so as to maximize reward and avoid unpleasant events. An individual with overly active LHb, such as in major depression, would be expected to be easily or continually disappointed and generally expect bad outcomes. The LHb receives inputs from the basal ganglia and the limbic system, and projects to aminergic midbrain centers including the serotoninergic dorsal raphe nucleus (DRN) and the dopaminergic ventral tegmental area (VTA), and also to the rostromedial tegmental nucleus (RMTg), a GABAergic nucleus strongly inhibiting dopamine centers. However, the contribution of individual LHb inputs and outputs in signal processing to control behavior, and how their dysfunctions may contribute to major depression is still elusive. Our previous work has shown that the pathway from the LHb to the RMTg plays an important role in motivational control, where its activation reduces motivation to exert effort. To examine potential alteration in synaptic transmission in this pathway in depression, we examined how chronic stress may impact synaptic transmission at this pathway. To this aim, we expressed ChR2 in the LHb, submitted mice to chronic social defeat stress (CSDS), and characterized synaptic transmission in the RMTg from control and stressed mice using whole-cell recordings. Similar approach has been used to also characterize transmission at the

DRN and VTA pathways. At the LHb-RMTg synapses, CSDS increased presynaptic transmission (decreased paired-pulse ratio) compared to control mice. At the LHb-DRN synapses, chronic stress did not change presynaptic transmission (PPR) but increased postsynaptic transmission (increased evoked AMPAr/NMDAr ratio) in susceptible mice. A large fraction of the potentiated neurons in the DRN were serotoninergic and clustered in a specific anteromedial subdivision of the DRN. Finally, at the LHb-VTA synapses, CSDS decreased AMPAr/NMDAr ratio in susceptible mice while no change was observed for the PPR. Interestingly, we also found that VTA-projecting neurons were less active in susceptible mice suggesting a hypofunctional reward circuit encompassing the LHb-VTA pathway. Taken together, these results suggest that the LHb neural outputs are differently altered following CSDS, and these synaptic changes may have distinct contribution to the development of maintenance of symptoms found in depressive disorders.

PS6.4 *Dorsal hippocampus neuronal activity during context fear discrimination*

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BACKGROUND AND AIM: Assessing an environment as safe or dangerous is critical for our survival and impairments in this process are a central criterion of post-traumatic stress disorder (PTSD). To develop treatments for PTSD, an understanding of the neuronal circuit activity that supports spatial representations and fear expression are necessary. METHOD: Here we investigate context fear discrimination using single-photon in vivo microendoscope calcium imaging in freely behaving mice during a novel context retrieval task. Using a cylindrical LED screen as a conditioning apparatus, we presented different visual contexts while mice remained in the same physical space. Mice were fear conditioned to visual context A in the AM and presented neutral context B in the PM. During the context memory retrieval test, mice were placed in the apparatus and context A and B presentations were repeatedly alternated while hippocampal activity and fear behaviour were recorded. RESULTS: We report three primary findings. During context fear memory formation, the hippocampal spatial map for context A is altered. Furthermore, "teleporting" mice between threatening context A and neutral context B is associated with dynamic alterations in the hippocampal spatial map. Finally, as spatial maps for threatening and neutral contexts become more distinct, context fear discrimination becomes stronger. CONCLUSIONS: Together these findings illustrate the dynamic hippocampal activity associated with context fear discrimination and provide a framework to understand how spatial representations are linked to emotional behaviors.

Parallel Symposium 7: Cueing Factors in Addiction

Sponsored by the Djavad Mowafaghian Centre for Brain Health

PS7.1 *Morphine learned as an interoceptive stimulus causes sex- and task-dependent alterations in subsequent morphine reinforcement and reward in rats.*

Jennifer Murray[1], Allyson Andrade[1], Caitlin Nolan[1], Adiia Stone[1]

[1]University of Guelph

Introduction: Research on drugs of abuse typically focuses on their reinforcing or rewarding effects and how surrounding proximal and distal cues can trigger drug seeking and taking behaviours. However, drugs also elicit internally perceived (interoceptive) stimuli that can be used as cues to guide appropriate behaviour, including how and when to seek food. Our research program investigates how such interoceptive cue-dependent learning with the mu opioid receptor agonist morphine can alter the subsequent value of that drug. Methods: Morphine is trained to disambiguate when a discrete exteroceptive auditory conditioned stimulus (CS) is predictive of a sucrose unconditioned stimulus (US). Male and female rats are injected with morphine or saline 15min before each 20min session. Every session contains 8 CS presentations. For feature positive (FP) training, morphine (3.2mg/kg) indicates when the CS-US contingency is active; on intermixed saline sessions, the US does not follow the CS. For feature negative (FN) training, the contingencies are reversed. Rats learn to seek sucrose during the CS presentations on appropriate sessions. Three recent studies have built on this effect: First, following discrimination training, we assessed the effects of the learning on morphine reinforcement by fitting rats with IV catheters to self-administer morphine (0.5mg/kg/infusion). Second, in a separate cohort, following discrimination, we assessed the effects of the learning on morphine reward by then shifting them to place conditioning. Under the standard discrimination training procedure, contingency learning can only be assessed on the first trial of each session, obfuscating the pattern of learning across the remaining trials. Therefore, in the third study, rats assigned to FP or FN groups underwent one-trial training in which a single CS was presented in each session. Results: In all standard discrimination training studies, rats were able to disambiguate morphine from saline conditions. Following training, FP male, but not female, rats self-administered more morphine, sought more morphine under extinction conditions, and showed greater reinstatement than FN rats. Conversely, there was no development of morphine conditioned place preference in FN female, but not male, rats. Finally, when assessing the development of the discrimination on a trial-by-trial basis, we are so far observing few differences between training contingency based on sex. Implications: These findings indicate that a prior appetitive or explicitly non-appetitive learning history with the stimulus effects of a drug of abuse can alter its subsequent reinforcement and rewarding value in a sex-dependent manner. Particularly in the case of opioid analgesics, such a finding has important implications for how such interoceptive stimuli may be differentially processed following drug experience in humans.

PS7.2 *Interoceptive correlates of acute alcohol administration and future clinical avenues*

Mateo Leganes-Fonteneau[1], Jennifer Buckman[1], Marsha Bates[1]

[1]Rutgers University

Interoception, the integration of bodily states in the brain, is hypothesized to support alcohol-related behaviors. However, there is little evidence on how cardiac interoceptive processes are affected by acute alcohol administration. Two sets of published studies examined how alcohol-induced changes in interoception shape alcohol-related responses. In two experiments (n=50, n=31) we found that alcohol modulates participants' ability to feel their own hearts, and that these changes correlate with perceived alcohol effects and mood changes. Further, changes in interoception correlate with anticipated effects of alcohol, as an index of alcohol expectancies. We propose that alcohol-induced interoceptive experiences build, over the course of drinking history, an expectancy about alcohol effects. These expectancies are in turn crucial for future drinking behaviors. Heart-rate variability indices allow studying the strength of heart-brain communication as a measure of interoceptive signaling. In an initial study (n=168) we found that, in participants with a family history of alcohol use disorder, cardiac signals and memories for alcohol stimuli correlated after alcohol administration. In a second study (n=31) we found that changes in cardiovascular states after alcohol administration correlate with alcohol attentional biases. This implies that alcohol effects on interoception support alcohol priming. These combined results build evidence for different interoceptive pathways underlying positive reinforcement mechanisms in addiction, and can help develop novel treatment and diagnostic tools within the growing field of embodiment and cognition.

PS7.3 *Differences in alcohol cue reactivity based on the social context*

Samuel Acuff[1], Bruce Bartholow[2], Jeffrey Sable[3], James MacKillop[4], James Murphy[1]

[1]The University of Memphis, [2]The University of Missouri, [3]Christian Brothers University, [4]McMaster University

BACKGROUND AND AIM: Drinking typically occurs in social settings, and emerging adults are more likely report binge drinking on nights with friends compared to nights when they are alone. However, those who report more solitary drinking episodes tend to have greater problems and an increased risk for alcohol use disorder. Behavioral economics suggests that heavy alcohol use may be most likely when the value of alcohol outweighs the costs. It is important to understand social effects on alcohol value, in addition to individual differences, which may explain variations in patterns of solitary drinking. Previous research found a 50% increase in alcohol value, using behavioral economic demand curves measured with alcohol purchase tasks, in a social, compared to solitary, drinking condition. Further, the difference in value across conditions predicted alcohol problems. It is unclear whether these findings correspond with underlying biomarkers of reward, creating a barrier in understanding behavioral and biological risk pathways. One biomarker candidate is the event-related potential

known as the P3, which is thought to reflect the incentive value of the eliciting stimuli. Harmful alcohol use is associated with greater P3 reactivity to alcohol than to neutral cues. However, no study has examined relations with alcohol demand, and little work has examined P3 reactivity to alcohol under social conditions compared to alcohol alone. METHODS: Mr. Acuff will present data from emerging adults (current n=37; anticipated N=60) who completed an oddball task during an EEG session and a solitary and social alcohol purchase task. RESULTS: Consistent with previous research, demand intensity (consumption at zero cost) for the solitary scenario (M=4.69, SD=2.41) was significantly lower than intensity for the social scenario (M=6.26, SD=3.42; Cohen's d=.66). Further, demand Omax (maximum monetary expenditure during the task) for the solitary scenario (M=20.60, SD=19.54) was significantly lower than Omax for the social scenario (M=27.86, SD=25.17; Cohen's d=.43). Preliminary analyses of available EEG data suggests greater P3 reactivity to social alcohol cues than to alcohol alone (Cohen's d=.30), but similar P3 reactivity to social alcohol cues and social nonalcohol (i.e., people hanging out, Cohen's d=.04). Relations between alcohol demand indices and P3 reactivity to social and nonsocial alcohol cues will be examined in the context of multilevel modeling. CONCLUSIONS: The results suggest that P3 may serve as a biomarker for changes in value that aggregates both alcohol and social value. P3 reactivity across cue conditions was consistent with alcohol demand data, which suggested that alcohol value is greater when drinking with peers than when alone. Additionally, P3 data revealed no difference in reactivity when removing alcohol from a social condition, suggesting that, much of the reward from drinking with friends may come primarily from peer connection.

PS7.4 *Contribution of cues to concurrent decision-making*

Justin Strickland[1], William Stoops[2], Cecilia Bergeria[1], Katherine Marks[2]

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Research on drug-related cues has historically focused on how cue exposure impacts measures related to substance use such as drug craving. Less studied in this context is how drug-related cues may impact decision-making between non-drug reinforcers made in events outside of drug-taking episodes. Clinically, changes in decision-making resulting from the presence of drug-related stimuli may help explain cascades of behavior in substance use disorder leading to high-risk activities and negative consequences that were otherwise considered disadvantageous without the addition of a discriminative cue for drug reinforcement. This talk will review recent studies evaluating a novel concurrent choice task designed as a laboratory model of cue-based decision-making. These studies collectively show how choice is a systematic and reliable predictor of substance use risk (e.g., severity of use and use-relate consequences), is specific to drug-cue contexts, and may help identify individual difference variables for individualized treatment. Future research will also be described using these methods in treatment contexts to determine how the value of drug-related cues is altered throughout the course of treatment, and how different treatment modalities may impact changes in value. An

interactive demonstration of the task with the audience will be conducted through the use of a mobile compatible task variation.

Parallel Symposium 8: Balancing Tensions between Proprietary Research, Open Neuroscience, and Human Rights

Sponsored by Vision: Science to Applications (VISTA) York University

PS8.1 *Primer on patenting of neurotechnologies from the Canadian perspective*

Zelma Kiss[1], Ari Rotenberg[2], Stacey Anderson-Redick[1], Judy Illes[2]

[1]University of Calgary, [2]University of British Columbia

Patents turn innovations into protected property to balance the interests of inventors and the public to encourage innovation. The invention must fit into four subject matter categories of process, machine, manufacture, or composition of matter. The innovation must be novel, useful, and non-obvious. It must enable a person of knowledge in the relevant field to practice the innovation; if it is vague such that a practitioner of ordinary skill could not use the information contained therein, and the knowledge common to the profession, to realize the promised useful result, then the patent is invalid. Natural phenomena, abstract ideas, and mental processes cannot be patented. Even if substantial work is put into the discovery of a mathematical formula or a new role for a brain region, neither by itself is patentable. In 2017 we performed a patent landscape analysis that identified brain regions in their claims. We discovered a large increase in such patents granted over recent years, as well as some with unreasonable and overly broad claims. The study led to a larger initiative examining patenting internationally, as part of an ERA-NET (Research Projects on Ethical, Legal and Social Aspects of Neuroscience) NEURON (Network for European Funding for Neuroscience Research) CIHR funded grant called The International Neuroethics Patent Initiative. According to the OECD, between 2008 and 2016, 16,273 patents representing a health-related neurotechnology were filed worldwide, with 58% being filed in the US and 63% about devices/methods for performing neuromodulation. While pure medical methods, or techniques without an associated novel device, are ineligible for patent protection in Canada and most other countries, they are patentable in the US. This has led to many international inventors patenting in the US, including Canadians. Examples will be discussed in the presentation. Medical method patenting may have ramifications on several groups: physicians by restricting the therapeutic tools available to them, patients by slowing release of and preventing access to new treatments, and researchers by limiting the scientific principles they may investigate. Neuroethical considerations are many: a patent that covers all or many practical ways of detecting and modulating the activity of a brain region runs the risk of being a patent on the brain region itself; protecting patent rights prior to proof of scientific validity encourages a patent-first ask-questions-later mentality; inventions that are likely to be most profitable may be developed before those that

may do more good; and, using patents as security allows them to devolve to companies that do not necessarily have an interest in health promotion. A system for patenting and marketing new invasive and non-invasive neurotechnologies that balances medical and commercial value, autonomy, and human use protections is critical. Proactive guidance from within the field is essential to achieve this balance.

PS8.2 *Insights from the DMCBH Open Science Initiative: an open science buy-in project in action*

Jeffrey LeDue[1], Judy Illes[1], Timothy Murphy[1], Paul Pavlidis[1]

[1]University of British Columbia

The UBC Djavad Mowafaghian Centre for Brain Health (DMCBH) Open Science Initiative is funded by McGill's Tanenbaum Open Science Institute as an open science "buy-in" project. The initiative launched Dec 1, 2021 and will run for 1 year with the objective to explore local support for open science and a framework that will align the DMCBH with Open Science initiatives at the McGill Neuro, Hotchkiss Brain Institute, Douglas Research Centre, and Western University. The Initiative at UBC is divided into 6 activities that marshal our Centre's existing strengths in open science and provide the basis and opportunity for iterative consultation, education, and planning. The 6 activities are: 1. A quarterly seminar series 2. Assessments, surveys, and town halls 3. Assessment of the impact of IP and attitudes toward Open Science 4. Open Research training and facilitation, including customized student-driven Databinge events 5. Engagement with university leadership 6. Development of the principles and an implementation plan Activities 1-4 are on-going and will inform Activities 5 and 6 in the second half of the project. Here, we provide an update on Activities 2 and 4. The Initiative's Open Scholarship Survey is designed for all members of the DMCBH research community regardless of area of specialization, and allows us to capture attitudes, behaviour and perceived norms with respect to key open science practices such as data sharing, code sharing, materials sharing, use of preprints, and open access publishing. Specific questions are posed about the perceived advantages and disadvantages of open science, including the approach to IP. Early results suggest that our community perceives open science as particularly important for neuroscience and is more focused on the perceived benefits to brain health stakeholders than any positive or negative impacts on IP. The ongoing Open Science Practices Needs Assessments are modelled after assessments undertaken in 2019 at UBC to create a resource to assist labs with Data Management and Data Sharing. The assessments consist of guided conversations with key personnel from individual labs (faculty, staff and students) and cover a range of questions from day-to-day data management practices to the active model for data stewardship including ethical, legal and intellectual property concerns. Results support the adoption and enhancement of open science practices through the student driven, data-centric Databinge forum. Overall, we expect a hybrid approach to Open Science at DMCBH that

embraces open principles while maintaining individual freedom to pursue some level of IP protection for certain elements of neuroscience progress.

PS8.3 *Neuromodulation Patents: a landscape analysis from 2016 through 2020*

Ari Rotenberg[1], Anna Nuechterlein[1], Ashley Lawson[1], Stacey Anderson-Redick[2], Zelma Kiss[2], Judy Illes[1]

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We aimed to analyze the progress of trends in patent construction first characterized by Roskams-Edris et al. (2017) for neuromodulation methods patents granted from 2016 through 2020. We developed a novel, customized search algorithm to scrape Lens.org, an open-access patent database designed to track trends in innovation and return patents in neuromodulation methods. Our approach was based on the presence of combinations of terms associated with the nervous system or its modulation in the text of claims. We applied a content analytical procedure to facilitate a standard review of the claims of each meeting inclusion criteria pertaining to nervous tissue and health-related applications. Results on patents with Canadian inventors, applicants, or owners are reported here. Overall, the algorithm returned 3,065 patents filed with the United States Patent and Trademark Office and European Patent Office. Of the 155 Canadian-driven patents in the sample, 26 met criteria for in-depth evaluation of medical feasibility and ethical considerations. These patents covered a range of techniques in stimulation, ablation, device installation, thermotherapy, and alternative medicine purporting to assess, treat, and monitor an underlying condition with varying degrees of invasiveness. We identified 76 direct references to regions of the nervous system and 136 references to underlying conditions. The terminology of these references did not adhere to any standardized labeling system, causing considerable ambiguity in some cases as to which particular regions or conditions were implicated in the method at hand. The majority of references in both categories were attributed to a small subset of the patents reviewed; one patent alone was responsible for 64 [47%] of references to underlying conditions. Results suggest that while proprietary overreach may be infrequent, it is extreme when it occurs.

PS8.4 *Perspectives on intellectual property protections and open neuroscience*

Ashley Lawson[1], Ari Rotenberg[1], Anna Nuechterlein[1], Paul Pavlidis[1], Jeffrey LeDue[1], Judy Illes[1]

[1]University of British Columbia

Patents protect the intellectual property (IP) of innovators for the purpose of establishing unique rights to a product, and enabling widespread adoption and investments for financial gain. In health care, patents conventionally protect innovations involving methods and devices, but protections of

naturally occurring products such as human tissue and brain regions have encroached on this domain over the past few years (Roskams-Edris et al., 2017). The principles and intentions of Open Science (OS) may challenge such protections in terms of benefit to research and clinical care, return of value to investors from the public sector such as government agencies, and even opportunities for training new generations of neuroscience leaders and inventors. Here we examined intersections between patenting and OS as perceived by neuroscience researchers, and specifically sought their insights into strategies for non-restrictive IP needed to resolve emerging tensions before they forestall progress. To gather these perspectives, we conducted a series of focus groups with researchers from the Centre for Brain Health at the University of British Columbia. We developed a semi-structured interview guide that covered three major areas: patents in general, patents and open science, patents in neuroscience. Six focus groups and three interviews were conducted in-person and virtually to accommodate researchers' schedules and University COVID requirements (N=29, 20 men, 9 women). Focus groups were organized according to the patent experience of participants: 11 were patent-experienced; 18 had little or no patent experience. All focus groups and interviews were recorded, transcribed professionally, and de-identified. We used the method of grounded theory to extract major themes Major emergent themes for IP were: advantages of IP, drawbacks of IP, changing IP landscape, conditionally appropriate use of IP, and current IP practices; for OS: advantages of OS, drawbacks of OS, current OS practices, impact of change, and potential for the coexistence of IP/OS; and for Ethical Considerations: cognitive integrity, neuro-exceptionalism, justice, responsibility, and virtue. All told, the data to date suggest that while IP is essential to many researchers, the benefits conferred by OS are significant. Participants suggest that there is no need to eliminate IP within OS, and emphasize potential avenues for hybridization between IP and OS that could mitigate the disadvantages of highly restrictive brain patents. References Roskams-Edris, D., Anderson-Redick, S., Kiss, Z. H., & Illes, J. (2017). Situating brain regions among patent rights and moral risks. Nature Biotechnology, 35(2), 119-121. https://doi.org/10.1038/nbt.3782

Parallel Symposium 9: Systemic Inflammation and the Brain: Interactions with Glia and Neurons

Sponsored by the Djavad Mowafaghian Centre for Brain Health

PS9.1 *The danger of brain infections: Microglia cell death is required for optimal immunity to Toxoplasma gondii in the CNS*

Samantha Batista[1], Isaac Babcock[1], Maureen Cowan[1], Katherine Still[1], Tajie Harris[1]

[1]University of Virginia

Control of infection within the central nervous system (CNS) is necessary to protect from damage that is often irreversible. The protozoan parasite Toxoplasma gondii causes a chronic infection of the brain that requires constant immune pressure to control parasite replication. Within the brain, T. gondii transitions to a dormant cyst form. For reasons that are not well-understood, cysts reactivate sporadically endangering neighboring cells. We find evidence of cell death in regions of cyst reactivation and a loss of CNS resident glia. We find that immune cells accumulate in these regions, suggesting that dying cells release factors that attract immune cells to specific locations in the brain. We specifically explored the importance of IL-1α, an alarmin that is expressed by microglia and monocyte-derived macrophages following T. gondii infection. We find that ASC specks form in microglia during infection, consistent with inflammasome activation. Moreover, microglia release IL-1α ex vivo while macrophages do not. The release of IL-1α is dependent on the pore forming protein gasdermin-D and the activity of caspase-1, supporting a role for microglia death by pyroptosis. Mice lacking IL-1α, IL-1R1, caspase-1/11, or gasderminD have higher parasite burdens and defects in the immune response to T. gondii in comparison to wildtype mice. Similarly, we find that deletion of caspase-1 from CX3CR1-expressing cells impacts host control of the parasite in the brain. Together, these results demonstrate that the detection of microglia cell death/damage is necessary to mount an immune response to a pathogen in the CNS.

PS9.2 *The potential contribution of systemic inflammation in neuropathic pain*

Ji Zhang[1], Wen Bo Sam Zhou[1], Xiang Qun Shi[1], Younan Liu[1], Simon Tran[1], Francis Beaudry[2]

[1]McGill University, [2]Universite de Montreal

Background: Neuropathic pain is a complex, debilitating disease that results from injury to the somatosensory nervous system. The presence of systemic chronic inflammation has been observed in chronic pain patients, but whether it plays a causative role remains unclear. Methods: We assessed the protein profile in the serum of mice following the partial sciatic nerve ligation (PSNL) or sham surgery using mass spectrometry-based proteomic analysis. We transferred PSNL or sham serum to naïve mice via intravenous injection and assessed mechanical and cold sensitivity by von Frey and acetone tests. To target a myriad of inflammatory mediators at once, we treated PSNL mice with bone marrow cell extracts (BMCE), having established broad anti-inflammatory properties. Results: Proteomic analysis of mouse serum at 1-day and 1-month following partial sciatic nerve injury (PSNL) or sham surgery revealed that nerve injury resulted in a long-lasting alteration of serum proteome, where the majority of differentially expressed proteins were in inflammation related pathways, involving cytokines/chemokines, autoantibodies and complement factors. While transferring sham serum to naïve mice did not change their pain sensitivity, PSNL serum significantly lowered mechanical thresholds and induced cold hypersensitivity in naïve mice. The treatment of PSNL mice with BMCE not only partially restored serum proteomic homeostasis, but also significantly

ameliorated PSNL-induced mechanical allodynia. Serum from BMCE-treated PSNL mice no longer induced hypersensitivity in naïve mice. Conclusions: These findings clearly demonstrate that nerve injury has a long-lasting impact on systemic homeostasis, and nerve injury associated systemic inflammation contributes to the development of neuropathic pain.

PS9.3 *The role of ependymal cells in regulating CNS inflammation*

Adam Groh[1], Nina Caporicci-Dinucci[1], Brianna Lu[1], Jo Stratton[1]

[1]Montreal Neurological Institute

Multiple Sclerosis (MS) is the most common demyelinating disease and is characterized by inflammatory and neurodegenerative components, where progressive neurological deficits currently represents the main source of disability. It is now recognized that the grey matter is profoundly impacted, and loss of volume (or atrophy) in deep grey matter (DGM) structures are the most consistent correlates of disease progression. A critical observation is that DGM is subject to atrophy that is more pronounced in areas exposed to cerebrospinal fluid (CSF), suggesting that factors from CSF, such as cytokines, might contribute to DGM damage. As an ECR, my research platform focuses on understanding CSF-associated drivers of neurodegeneration with an emphasis on understanding the involvement of cells that line CSF exposed brain regions, known as ependymal cells in the ventricular system. We have performed advanced single cell transcriptomics and identified several ligand-receptor binding partners relevant to disease. We have also demonstrated that ependymal cells are particularly vulnerable to acute and chronic inflammatory insults, including undergoing gliosis and losing barrier functions. Importantly, we have developed in vitro and in vivo assays to determine which inflammatory factors may be underling these effects. By better understanding the mechanisms underlying disease progression, we aim to discover novel therapy targets to better treat MS.

PS9.4 *Versican as a potential inhibitor of remyelination: proposed mechanisms through impeding oligodendrocytes and promoting Th17 cytotoxic neuroinflammation*

Samira Ghorbani[1], Emily Jelinek[1], Rajiv Jain[1], Cenxiao Li[1], Brian Lozinski[1], Susobhan Sarkar[1], Deepak Kaushik[1], Yifei Dong[1], Thomas Wight[2], Soheila Karimi-Abdolrezaee[3], Geert Schenk[4], Jeroen Geurt[4], Eva Strijbis[4], Chang-Chun Ling[1], V.Wee Yong[1]

[1]University of calgary, [2]Benaroya Research Institute, [3]University of Manitoba, [4]MS Center Amsterdam

Remyelination failure in multiple sclerosis (MS) contributes to progression of disability. The deficient repair results from neuroinflammation and deposition of inhibitors including chondroitin sulfate

proteoglycans (CSPGs). Which CSPG member is repair-inhibitory or alters local inflammation to exacerbate injury is unknown. Here, we correlate high versican-V1 expression in MS lesions with deficient premyelinating oligodendrocytes, and highlight its selective upregulation amongst CSPG members in experimental autoimmune encephalomyelitis (EAE) lesions that model MS. In culture, purified versican-V1 inhibits oligodendrocyte precursor cells (OPCs) and promotes T helper 17 (Th17) polarization. Versican-V1-exposed Th17 cells are particularly toxic to OPCs. In NG2CreER:MAPTmGFP mice illuminating newly formed GFP+ oligodendrocytes/myelin, difluorosamine (peracetylated,4,4-difluoro-N-acetylglucosamine) treatment from peak EAE reduces lesional versican-V1 and Th17 frequency, while enhancing GFP+ profiles. We suggest that lesion-elevated versican-V1 directly impedes OPCs while it indirectly inhibits remyelination through elevating local Th17 cytotoxic neuroinflammation. We propose CSPG-lowering drugs as dual pronged repair and immunomodulatory therapeutics for MS.

Parallel Symposium 10: Sleep perturbations in Alzheimer's disease patients and animal models

PS10.1 *Cognitive, histological, and transcriptional correlates of sleep fragmentation in older adults*

Andrew Lim[1]

[1]University of Toronto

BACKGROUND AND AIM: Sleep and circadian rhythm disruption are common in older adults and may have a bidirectional relationship with cognitive impairment and dementia. Here, I will review some of our data relating sleep disruption to dementia-associated brain changes in community-dwelling older adults. METHODS: We studied 1080 older adults from 2 community-based cohort studies of aging. We quantified antemortem sleep and circadian rhythmicity using multi-day wrist accelerometry and cognitive function using a battery of 21 neuropsychological tests spanning 5 domains and then related this to postmortem dementia-related histological findings, and to gene expression in the dorsolateral prefrontal cortex assessed by bulk tissue RNA-seq. RESULTS: Greater antemortem sleep fragmentation is associated with more rapid antemortem cognitive decline, and a higher risk of incident Alzheimer's disease. As well, it is associated with a higher burden of arteriolosclerosis, a higher burden of neurodegenerative pathologies like levy bodies and neurofibrillary tangles, and greater expression of genes characteristic of aged microglia and activated astrocytes. CONCLUSIONS: Sleep fragmentation is associated with more rapid cognitive decline and multiple dementia-associated neurodegenerative, vascular, and transcriptional brain changes in older adults. Sleep disruption may be a contributor, or marker of, key dementia-associated brain changes.

PS10.2 *Ambulatory EEG sleep monitoring in Alzheimer disease: A Pilot Study*

Amelia Casciola[1], Meghan Chen[1], Penny Slack[1], Ali Kazemi[2], Maryam Mirian[1], Jason Valerio[1], Martin McKeown[1], Howard Feldman[3], Haakon Nygaard[1]

[1]University of British Columbia, [2]Univ. of California, Davis, [3]University of California San Diego

BACKGROUND AND AIM: Sleep disturbances are common in Alzheimer's disease (AD), with estimates of prevalence as high as 65% across AD and Mild Cognitive Impairment (MCI). A major limitation to a formal, qualitative assessment of sleep in these populations is the requirement for inpatient polysomnography (PSG), which is often not well tolerated in patients with dementia. We have recently developed a deep learning model to reliably analyze lower quality EEG data obtained from a simple, 2-lead EEG headband. This methodology allows for ambulatory assessment of sleep, with the potential for more widespread sleep staging particularly in vulnerable populations. Here we present a pilot study of ambulatory EEG sleep assessment in patients with AD and non-demented control subjects. METHODS: A total of 23 AD patient and 22 age-matched, non-demented control subjects underwent ambulatory EEG. Each subject wore the headband for up to 3 nights. A deep learning model was previously developed by our group in healthy volunteers undergoing both PSG as well as headband EEG recordings. RESULTS: AD patients were shown to have less N3 sleep than control subjects ($p<0.05$, t-test). No differences were found in N2 or REM sleep stages. Actigraphy supplementing the EEG will be presented. CONCLUSIONS: We show that ambulatory EEG is feasible in patients with AD. Moreover, using a deep learning model, relatively low quality, 2-lead EEG headband data can stage sleep in an ambulatory setting. Similar to studies using PSG, we find that N3 sleep is reduced in patients with AD. Our findings suggest that ambulatory EEG is a promising approach for future studies addressing sleep quality in patients with dementia.

PS10.3 *Potential role of orexin receptor antagonists in the treatment of sleep disorders associated with Alzheimer's disease*

Jane Yardley[1], Jocelyn Cheng[1]

[1]Eisai, Ltd

BACKGROUND AND AIMS: Many patients with Alzheimer's disease (AD) display circadian rhythm and sleep-wake disturbances. Even in those at risk for AD, worse subjective sleep quality, more sleep problems, and daytime sleepiness have been associated with greater AD pathology (increased Aβ and tau). In turn, the disturbed sleep can exacerbate cognitive difficulties associated with AD. As AD progresses, the common sleep disorder is Irregular Sleep-Wake Rhythm Disorder (ISWRD), in which sleep is fragmented, and unplanned naps occur during waketime. These disturbances often lead to a

decision to institutionalize. METHODS: There are no pharmacologic treatments currently approved specifically to treat the sleep disturbances associated with AD. The American Academy of Sleep Medicine (AASM) strongly recommends against the use of sedative hypnotics in these patients because of safety concerns, including increased risk of falls. To address the unmet medical need, investigations began regarding the potential use of an alternative class of sleep-promoting drugs, the dual orexin receptor antagonists (DORA), lemborexant and suvorexant, in patients with AD and ISWRD or with insomnia, respectively. RESULTS: These studies followed the findings from animal models that chronic sleep restriction accelerates Aβ plaque burden, while enhancing sleep via orexin receptor blockade markedly inhibits Aβ plaque accumulation. While few mouse AD models exhibit the sleep-wake fragmentation observed in ISWRD, lemborexant has been studied in senescence-accelerated mouse prone-8 (SAMP8) mice, which are a model for these disturbances in AD, and which display several aspects of sleep-wake and rhythm disturbances in AD, notably mistimed activity. CONCLUSIONS: In this presentation, the evidence for the role of orexin in the neuropathological changes associated with AD will be discussed, as well as the use of orexin receptor antagonists as potential therapeutic options.

PS10.4 *Alterations in wakefulness and sleep quality in animal models of amyloid-beta derived neurodegeneration*

Jonathan Brouillette[1], Audrey Hector[1], Chloé Provost[1], Karl Fernandes[2], Valérie Mongrain[1]

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Amyloid-beta oligomers (Aßo) derived from Aß1-42 peptides are the most neurotoxic species and correlate extensively with memory deficits in AD patients and animal models. Soluble Aßo begin to accumulate in the human brain approximately 10 to 15 years before any clinical symptoms of the disease and are implicated in synapse and neuronal losses at the onset of AD. Although we know that sleep perturbations are among the first clinical symptoms of AD, the specific impact of soluble Aßo on sleep features remains to be determined. Here, we performed chronic hippocampal injections of soluble Aß1-42 oligomers in rats to determine the progressive impact of amyloid pathology on sleep architecture and on the various oscillatory activities of the brain using electroencephalographic (EEG) measurements. We found that Aßo-injected rats and control rats injected with scrambled Aß spent the same amount of time in wakefulness, slow-wave sleep (SWS) and paradoxical sleep. Interestingly, Aßo increased slow-wave activity (SWA) and low-beta activity during wakefulness, and decreased theta and alpha activity during SWS. These differences were significant for the frontal cortex but not for a central recording site. Analyses are underway to determine if these changes are also observed in the transgenic 3xTg-AD mouse model, and if these alterations can be reversed by a lipid-modulating pharmacological treatment. Identifying the specific signature of Aßo on sleep features might serve as a non-invasive and cost-effective marker for the diagnosis of early AD, and as an outcome measure

for new AD therapies that would be efficient before neurodegeneration causes permanent brain damage and severe memory losses.

Parallel Symposium 11: Canadian Cannabis and Psychosis Research Team (CCPRT): Multi-disciplinary investigations of the underlying neurobiology of the link between cannabis and psychosis

PS11.1 *Impact of cannabis use on brain maturation in a Canadian longitudinal cohort*

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Adolescence is a time of behavioural change, brain maturation and of increasing incidence of psychiatric illnesses. Adolescent exposure to cannabis is associated with increased risks for numerous adverse mental health outcomes including elevated risk for development of psychotic disorders. The impact of adolescent cannabis exposure on brain maturation is poorly understood. Cross-sectional studies and follow-up designs provide evidence for changes in brain structure of adolescent cannabis users but reports vary in the direction of such changes. Few studies have examined brain structure and cannabis use at more than two time points, however additional time points permit us to examine, in the same individuals, differences in brain structure in the presence of absence of a given risk factor such as cannabis use. We used a longitudinal design and participants from a population-based cohort study (n=3871) to study substance use, mental health symptoms, and brain maturation. Participants completed assessments for substance use, psychiatric symptoms for 5 years starting at age 13. Participants in the neuroimaging sub-cohort (n=150) completed structural MRI scans at three time points for each participant (at ages 13, 15, and 17). MRI images were processed using the ENIGMA consortium's Freesurfer longitudinal neuroimaging pipeline to quantify cortical thickness and the volumes of subcortical structures. Substance use was assessed using the DEP-ADO and timeline follow-back. We applied random intercept cross-lagged panel models to investigate temporal precedence in the relationship between cannabis and changes in brain structure. This presentation will discuss preliminary analyses of this cohort examining the relationship between cannabis use and brain structure, including roles of sex and age of cannabis exposure. This talk will also discuss follow-up analyses designed to answer questions about the relevance of these findings to our understanding of the impact of cannabis exposure on mental health and brain maturation.

PS11.2 *Sexually dimorphic effects of THC in adolescence: from dysregulation of dopamine guidance cues to changes in cognitive control*

Giovanni Hernandez[1], Tanya Capolicchio[2], Katherina Estrada[2], Emelie Dubé[2], Cecilia Flores[3]

[1]Douglas Research Institute, [2]McGill University, [3]Douglas Research Institute/McGill University

Cannabis is one of the most consumed substances among adolescents in North America. Its regular use during this developmental period is linked to an increased risk of cognitive impairments and psychiatric disorders later in life. However, the cellular and molecular processes underlying these effects, particularly the developing adolescent mesocorticolimbic dopamine system, remain unknown. Dopamine maturation in adolescence is mediated by the Netrin-1 guidance cue receptor, DCC, whose expression is controlled by the microRNA, miR-218. In previous research, adolescent male mice exposed to an abuse-like dose of amphetamine showed an upregulation of miR218 and a concomitant reduction of Dcc mRNA levels in the ventral tegmental area (VTA). These changes disrupt mesocorticolimbic dopamine development and cognitive control in adulthood. Here we assessed whether tetrahydrocannabinol (THC), the main psychoactive component of cannabis, alters the miR-218/DCC system in both male and female adolescent mice. Adolescent male and female C57/Bl6 mice (postnatal day 22) received intraperitoneal injections of THC, either 0, 2.5, 5, or 10 mg/kg, once every other day, for 10 days. One week after the last injection, miR-218 and Dcc mRNA expression were measured in the VTA using quantitative PCR (qPCR). In males, exposure to 5 and 10, but not 2.5 mg/kg THC, downregulated miR-218 in the VTA, inducing a concomitant increase in VTA Dcc mRNA levels. These changes are associated with improved stop impulsivity in the Go/No Go task in adulthood, similar to previous findings with a therapeutic-like dose of amphetamine. In contrast, THC did not alter miR-218 expression in females, but an increased Dcc mRNA level was observed following 5 and 10mg/kg dose. Females did not show changes in stop impulsivity in adulthood. In both males and females, THC exposure leads to dose-specific deficits in waiting impulsivity, wherein males pretreated with THC 5mg/kg show an increase in premature responses, females show similar results when pretreated with THC 2.5 mg/kg. Taken altogether, these results indicate that THC during adolescence impacts the molecular mechanisms controlling the development of mesocorticolimbic dopamine neurons in a sex-specific manner. In males, the epigenetic process by which THC mediates the netrin-1/Dcc system is via miR-218, the process for females remains to be elucidated. The effects of THC, in males cognitive control are dissociable, wherein there is an improvement in stop impulsivity but a deficit in waiting impulsivity.

PS11.3 *Anxiety mediates the relationship between cannabis use frequency and psychotic-like experiences in emerging adult females*

Haley Bernusky[1], Philip Tibbo[1], Fakir Yunus[1], Patricia Conrod[2], Matthew Keough[3], Kara Thompson[4], Marvin Krank[5], Sherry Stewart[1]

[1]Dalhousie University, [2]Université de Montreal, [3]York University, [4]St. Francis Xavier University, [5]University of British Columbia Okanagan

BACKGROUND AND AIM: Cannabis is commonly used by Canadian emerging adults (18-25 years), many of whom attend post-secondary education. Frequent cannabis use has been linked with psychotic-like experiences (PLEs); the exact nature of this relationship remains unclear. Anxiety is prevalent in emerging adults and has been independently linked with both cannabis use and PLEs. Females are more susceptible to anxiety and males to both cannabis use and PLEs. We evaluated whether anxiety mediates the relationship between cannabis use frequency and PLEs in emerging adult undergraduates. We also tested for moderation of this anxiety mediational model by biological sex. We had 3 hypotheses: H1) more frequent cannabis use would be associated with more anxiety which, in turn, would be associated with greater PLEs; H2) this anxiety-mediated path would prove stronger in females; and H3) the direct path from frequent cannabis use to PLEs would be stronger in males. METHODS: A sample of 1,507 first- and second-year emerging adult university students (mean [SD] age = 19.2 [1.52] years; 67% female) were recruited. Cross-sectional, self-report survey data were collected in fall 2021 from 5 Canadian universities as part of the UniVenture study. Validated measures capturing demographics, cannabis use frequency, anxiety, and PLEs were used. RESULTS: A mediation model with cannabis use frequency as the predictor, PLEs as the outcome, and anxiety as the mediator was tested, followed by a moderated mediation model with biological sex moderating the paths from frequent cannabis use to anxiety and from frequent cannabis use to PLEs. Models were tested using the SPSS PROCESS macro with bootstrapping and 95% confidence intervals. In the first model, consistent with H1, we found evidence of a significant indirect effect of cannabis use frequency on PLEs via anxiety (a-path $p < .001$; b-path $p < .001$; 95% CI [.016, .048]); no direct effect was found (c'-path $p = .946$) suggesting the relationship of cannabis to PLEs is fully mediated by anxiety. In the second model, significant moderated mediation was found (95% CI [.005, .060]). More frequent cannabis use was associated with increased anxiety among females only. According to conditional indirect effects, mediation through anxiety was significant for females (95% CI [.020, .056]), but not males (95% CI [-.015, .028]), consistent with H2. No significant sex moderation was found for conditional direct effects of cannabis on PLEs: the direct effect was not significant for either males ($p = .667$) or females ($p = .907$). Thus, contrary to H3, the cannabis use frequency to PLEs path was not stronger for males than females. CONCLUSIONS: Assuming replication in prospective research, results highlight anxiety as an important intervention target in frequent cannabis users, particularly females, to potentially prevent PLEs, and in turn psychosis, in emerging adults.

Parallel Symposium 12: Arousal related brain circuits and their role in sensory processing and behaviour.

Sponsored by CERVO Brain Research Centre

PS12.1 *Spatiotemporal dynamics and targeted functions of locus coeruleus norepinephrine*

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The locus coeruleus (LC) serves as the primary source of norepinephrine (NE) in the brain with a highly divergent set of projections to cortical and subcortical areas. The LC-NE system has been generally linked to sleep and arousal, and stress-related behaviors, in addition, at least two distinct roles have emerged with respect to learned behavior. LC activity controls action and sensory gain, and LC activity is linked with learning. Whether and how LC-NE activation facilitates these different components of learned behavior is unknown. Here, I will discuss our recent results showing that LC-NE activity displays distinct spatiotemporal dynamics to support separate functions during learned behavior. To do so, we used a behavioral task in mice with graded auditory stimulus detection and task performance. Optogenetic inactivation of the LC demonstrated that LC-NE activity was causal for both task execution and optimization. Targeted recordings of LC-NE neurons using photo-tagging, two-photon micro-endoscopy and two-photon output monitoring, showed that transient LC-NE activation preceded behavioral execution and followed reinforcement. These two components of phasic activity were heterogeneously represented in LC-NE cortical outputs, such that the behavioral response signal was higher in the motor cortex and facilitated task execution, whereas the negative reinforcement signal was widely distributed among cortical regions and improved response sensitivity on the subsequent trial. With this study, we demonstrate two concurrently encoded functions for the LC-NE system, namely task execution and performance optimization. Furthermore, we provide the first direct evidence that, at the level of LC-NE outputs, functional modularity exists and supports, at least partially, distinct aspects of learned behavior.

PS12.2 *The role of hypocretin/orexin neurons in social behaviour*

Derya Sargin[1]

[1]University of Calgary

Intraspecific social interactions are integral for survival and maintenance of society among all mammalian species. Yet, our understanding of the neural systems and mechanisms involved in the establishment of social connectedness and the consequences of the detrimental effects of social isolation are limited. Since their initial discovery as regulators of sleep/wakefulness and appetite in

the brain, the hypocretin/orexin neurons have also been shown to play an essential role in modulating energy homeostasis, motivated and emotional behaviour. These neurons are located exclusively in the hypothalamus that regulates complex and goal-directed behaviours. The hypothalamus has previously been shown to play an important role in the modulation of social behaviour by encoding internal states. My lab investigates how the hypothalamic hypocretin/orexin neurons and their downstream circuits participate in social behaviour. We identified hypocretin/orexin neurons to exhibit a robust increase in activity in response to social interaction. We demonstrate that the activity of hypocretin/orexin neuron population is differentially encoded during interaction between familiar and stranger conspecifics. Moreover, the optogenetic inhibition of hypocretin/orexin neuron activity during social behaviour or systemic injection of hypocretin/orexin receptor antagonist prior to social behaviour leads to a reduction in the amount of time mice are engaged in social interaction. Together, these data situate the hypocretin/orexin system as the part of a larger network that plays an integral role in the modulation of social behaviour. Here, we will additionally discuss the implications of these findings in an animal model of chronic social isolation that develops long-term social impairments.

PS12.3 *Interneuron contributions to state-dependent sensory processing*

Katie Ferguson[1], Jenna Salameh[1], Jessica Cardin[1]

[1]Yale University

BACKGROUND AND AIM: Visual information from the environment is rapidly and dynamically processed by a complex network of cortical neurons. Cortical activity patterns reflect not only changing sensory inputs, but also behavioral state (e.g., quiet wakefulness vs. active locomotion). Several lines of evidence suggest that inhibitory GABAergic interneurons (INs) may be key regulators of flexible cortical function. However, cortical GABAergic INs comprise several reciprocally connected, highly diverse subpopulations that are differentially activated during distinct states. One prominent model for state-dependent activation of cortical pyramidal neurons involves their disinhibition via arousal-activated vasoactive intestinal peptide-expressing INs (VIP-INs). These cells are hypothesized to suppress the activity of downstream INs (primarily somatostatin -expressing interneurons, or SST-INs), and consequently disinhibit pyramidal neurons. However, SST-INs are also activated by arousal, and target other IN populations. Thus, this dis-inhibitory model largely fails to account for the complex and context-dependent interactions among IN populations, leaving the role of distinct IN populations within the active cortical network largely unexplored. METHODS: We use two-photon calcium imaging in the primary visual cortex of awake behaving mice to identify cell type-specific GABAergic IN contributions to sensory processing, and to determine how behavioral state modulates the impact of GABAergic inhibition. To examine the state- and context-dependent role of IN-IN interactions, we used intersectional genetic tools to target two distinct IN populations simultaneously, focusing on the interactions between VIP-INs and its postsynaptic targets, SST-INs and pyramidal neurons.

Furthermore, through both chronic and acute manipulations, we assessed the role of VIP-INs in perceptual learning using a visual detection task. RESULTS: Our data suggest a complex spatiotemporal pattern of IN-IN interactions within the local cortical circuit. We find that VIP-INs contribute to state-dependent regulation of functional connectivity and make an unanticipated contribution to SST-IN visual response properties. Our findings suggest that the unidirectional linear dis-inhibitory circuit model is not sufficient to explain the impact of VIP-IN activity on the network during visual encoding. Furthermore, we find that VIP-INs play an important role in enhancing state-dependent visual perception. CONCLUSIONS: By examining IN-IN interactions in awake behaving mice, we uncover a complex role for VIP-INs in regulating large-scale changes to sensory processing and visual perception across behavioral states.

PS12.4 *Investigating the role of the claustrum in the control of behavioral state*

Jesse Jackson[1], Alison Do[1], Brian Marriott[1]

[1]University of Alberta

The claustrum is a small hyper-connected subcortical brain region. Despite intensive investigation, the precise function of the claustrum remains unclear. Excitatory outputs of the claustrum are topographically organized, with different neurons projecting to different cortical regions. We monitored the activity of these different claustrum outputs in head-fixed mice running on a treadmill and during sleep, using fiber photometry and two-photon calcium imaging. We found that separate claustrum output pathways are differentially recruited by transitions between rest and locomotion. Using pathway specific optogenetic activation, we also found that stimulation of claustrum neurons projecting to different cortical regions produces different changes in locomotor behavior and arousal as measured by pupil diameter. Our data indicate that discrete sets of claustrum neurons may have dissociable or complimentary roles in shaping the control of behavioral state.

Poster sessions

Poster Session 1: May 13, 2022

1A. Development

P1-A-1: *Investigating the mechanism of programmed cell death of hippocampal Cajal-Retzius cells*

Zain Patel[1], Mi Wang[1], Qiumin Tan[1]

[1]University of Alberta

Cajal-Retzius (CR) cells are a group of excitatory neurons that play crucial roles in the development of many structures in the brain including the hippocampus. They first arise around day 10-12 of embryogenesis. Starting from postnatal day 8 (P8), the vast majority of CR cells undergo programmed cell death (PCD). Most CR cells die via apoptosis. However, hippocampal CR cells die by a different, unknown mechanism. The goal of this project is to identify the mechanism by which hippocampal CR cells undergo PCD. Preliminary data have indicated that knockout of the transcriptional repressor, capicua (Cic), in CR cells leads to abnormal persistence of CR cells in the adult hippocampus. Hence, we will use Cic knockout mouse models to identify the cell death mechanism of hippocampal CR cells. We will test for markers of non-apoptotic mechanisms of cell death such as autophagy-dependent cell death or necroptosis. Immunostaining will be conducted on brain sections from mice of ages between P5 and P20 to assess changes in expression of markers over time. Additionally, we will use immunoelectron microscopy to evaluate subcellular structures of CR cells to gain clues about their cell death mechanisms. The results of this research will contribute to the understanding of developmental cell death. We can also better understand the roles of CR cells in normal development and in diseases and identify strategies to overcome abnormal CR cell death regulation.

P1-A-2: *The role of 14-3-3 proteins in oligodendrocyte development*

Luyang Hua[1], Ricardo Alchini[1], Alyson Fournier[2]

[1]McGill University, [2]Montreal Neurological Institute, McGill University

The development of higher-order nervous system functions found in vertebrates is dependent on myelination, which provides the means for rapid and energy-efficient saltatory conduction. In the central nervous system, myelination is mediated by oligodendrocytes that are derived from oligodendrocyte precursor cells (OPCs). The Fournier lab has identified the 14-3-3 family of adaptor proteins as potential regulators of oligodendrocyte maturation. The 14-3-3 family is comprised of

seven different isoforms that are highly conserved and ubiquitous in eukaryotic organisms. 14-3-3s bind specific serine- and threonine-phosphorylated motifs on client proteins, resulting in positive or negative regulation of client protein stability and function. While 14-3-3s are known to be expressed in white matter and oligodendrocytes, the role of 14-3-3s in oligodendrocytes has yet been fully examined. During in vitro differentiation of OPCs derived from rat glial culture, we saw that inhibition of 14-3-3 protein-client protein interactions by BV02, drug inhibitor of 14-3-3 protein-client protein interactions, increased membrane area and process complexity of the resulting oligodendrocytes without affecting the number of OPCs or oligodendrocytes. Similarly, in vitro lentiviral shRNAmir knockdown of individual 14-3-3 isoforms during OPC differentiation also increased membrane area and process complexity of the resulting oligodendrocytes. These results suggest a negative role by the 14-3-3-client interactions on oligodendrocyte membrane area and process complexity during oligodendrocyte maturation.

P1-A-3: *Investigating metabolic defects in 16p11.2-deficient primary mouse brain endothelial cells*

Julie Ouellette[1], Shama Naz[1], David Patten[1], Baptiste Lacoste[1]

[1]University of Ottawa

Brain development and function are highly reliant on adequate development and maintenance of vascular networks. As such, early impairments in vascular health can lead to neurodevelopmental defects. Very few studies have considered the role of the brain vasculature in autism spectrum disorders (ASD). ASD are neurodevelopmental conditions associated with genetic origins such as the common 16p11.2 deletion, which leads to haploinsufficiency of ~30 genes. We recently revealed that the 16p11.2 deletion induced endothelial-dependent structural and functional vascular abnormalities in the mouse brain, establishing a novel link between vascular impairments and ASD. While we now know that the 16p11.2 deletion leads to endothelial dysfunction, the mechanisms leading to these dysfunctions remain unknown. To address this knowledge gap, we used metabolomics and assessed mitochondrial parameters to decipher core features of brain endothelial cells (ECs) isolated from 16p11.2-deficient and wild-type (WT) mice. We identified a lower concentration of metabolites in 16p11.2-deficient ECs compared to WT ECs. Notably, 16p11.2-deficient ECs displayed an energetic failure with a 50% reduction of high energy metabolites including ATP, CTP, GTP, and UTP, which are all critical energy fuels required for the maintenance of cellular processes. Currently, we are attempting to rescue these phenotypes by targeting various pathways. This study will identify new players in ASD pathogenesis, a pre-requisite for the development of transformative therapeutic strategies.

P1-A-4: *Vesicular zinc modulates cell proliferation and survival in the developing hippocampus*

Selena Fu[1], Ashley Cho[1], Simon Spanswick[1], Richard Dyck[1]

[1]University of Calgary

In the brain, vesicular zinc, which refers to a subset of zinc that is sequestered into synaptic vesicles by zinc transporter 3 (ZnT3), has extensive effects in neuronal signaling and modulation. To date, vesicular zinc-focused research has mainly been directed to its role in the hippocampus, particularly its role in adult neurogenesis. However, whether vesicular zinc is involved in modulating neurogenesis during the early postnatal period has been less extensively studied. To provide insight into vesicular zinc's role in early developmental hippocampal neurogenesis, we used the ZnT3 knockout (KO) mouse model that lack vesicular zinc to evaluate cell proliferation and survival. Male and female ZnT3 KO and wildtype (WT) mice received bromodeoxyuridine (BrdU) injections at either postnatal day (P) 6, 14, or 28. Half of the pups from each group were killed 24 hours after the last injection to assess cell proliferation, as assessed by BrdU+ cells, and the other half were left to survive until P60 to assess cell survival. Our results show that male ZnT3 KO mice have impaired cell proliferation at P14, but the survival of these cells are sustained until P60, suggesting loss of vesicular zinc may impair normal cell proliferation and cell pruning at this age. At P28, we found sex-dependent differences whereby male mice, regardless of genotype, showed higher levels of cell proliferation. In conclusion, our findings offer novel insight into how vesicular zinc may modulate hippocampal neurogenesis during early postnatal development that may differ from its role in adult neurogenesis.

P1-A-5: *Investigating the role of the claustrum in regulating the development of cortical networks*

Tarek Shaker[1], Jesse Jackson[1]

[1]University of Alberta

The claustrum (CLA) is a small subcortical nucleus that is extensively interconnected with high-order brain centres, primarily the prefrontal cortex (PFC). Recent evidence suggests that innervation between the CLA and the PFC is implicated in complex cognitive processes, such as consciousness and attention. Nevertheless, the developmental time course of circuit maturation within the CLA as well as the formation of synaptic connections between the CLA and the PFC remains elusive. To investigate this, we injected anterograde and retrograde neural tracers into the PFC of Ai9 mice at seven-day intervals from postnatal day (P) 1 up to P49, and assessed the number of florescent cells 14 days post injection. We found that while the majority of CLA-PFC projections are established by P14, PFC-CLA projections do not fully develop until after P28, thus suggesting that CLA inputs may contribute to postnatal development of local PFC networks. Immunohistochemical analysis of CLA-specific markers between P1 and P60 revealed distinct maturation trajectories among different cell types. Excitatory neurons and somatostatin-expressing inhibitory neurons largely mature by P7. On the other hand, parvalbumin-expressing (PV+) inhibitory neurons are absent up to P14, but their number increases

between P21 and P35. Of note, the onset of PV expression in the CLA appears to be corollary to the establishment of PFC-CLA projections. This may suggest that maturation of PV+ inhibitory neurons in the CLA is gated by the excitatory synaptic drive of PFC inputs. We are currently performing electrophysiological recordings in the PFC and the CLA to characterize their respective physiological changes that correspond to the anatomical development of CLA-PFC and PFC-CLA connections.

P1-A-6: *Sex differences in dendritic morphology in the valproic acid (VPA) model of Autism Spectrum Disorders*

Olivia Williams[1], Cecilia Micelli[1], Melissa Perreault[1]

[1]University of Guelph

Autism Spectrum Disorders (ASD) display sex differences in prevalence, etiology, and presentation. Little research has elucidated mechanisms underlying these differences. Glycogen synthase kinase-3β (GSK-3β) is downregulated in the brain of VPA rats, implicated in disorders of cognitive impairment, and can regulate neuronal morphology. In this study, sex differences in morphology, and expression/activity of GSK-3a/β were evaluated. Pregnant rats were injected VPA (500mg/kg) or saline, and cortical and hippocampal tissue was dissected from pups. Cells were stained for Sholl or collected for Westerns on DIV 21. In Sholl, mean number of intersections for both male and female VPA cortical cells were lower than controls, dependent upon distance from the soma (males 80-130μm, p=0.001; females 30-100μm, p=0.005). In VPA hippocampal neurons, males had greater intersections between 50-100μm (p=0.021). In VPA females, there was a reduction at 10-30μm (p=0.009) and increase 90-200μm intersections from the soma (p=0.046), compared to controls. Analysis of length displayed only female VPA cortical neurons were reduced (p=0.029) compared to controls. Phosphorylation of GSK-3a/β (decreased activity) was higher in the cortex for male and female VPA neurons and higher in VPA females only in the hippocampus. Total GSK-3a/β expression in males and females was lower in VPA cortical and hippocampal cells. Therefore, sex and model-specific differences in morphology and GSK-3 activity in cortical and hippocampal VPA neurons are observed, which may be relevant to known differences in behaviour.

P1-A-7: *Maternal exposure to prostaglandin E2 affects dendritic morphology during hippocampal development - link to autism*

Shalini Iyer[1], Ilham Abbasi[1], Ashby Kissoondoyal[1], Dorota Crawford[1]

[1]York University

Prostaglandin E2 (PGE2) is a bioactive lipid molecule involved in normal brain development. Abnormal PGE2 levels due to exposure to environmental factors has been linked to autism spectrum disorders (ASDs). This study investigates sex-dependent effects of maternal PGE2-exposure at gestational day 11 (G11) on dendritic morphology in the developing hippocampus of C57BL/6J mice offspring. We previously established PGE2-exposed offspring exhibit sex-dependent ASD-like symptoms. We used the Golgi-Cox staining method to compare the hippocampi of PGE2-exposed male and female (PGE2M and PGE2F) offspring at postnatal day 30 (PN30) and 90 (PN90). Confocal microscopy followed by image analysis using ImageJ was used to examine dendritic arborization, length, branch order, cross-sectional area of the soma and the likelihood of observing dendritic loops. Compared to matched WT controls PGE2M and PGE2F have greater dendritic arborization further from the soma, with PGE2F having increased primary branching at PN30. However, at PN90 PGE2M have increased arborization closer to the soma, with greater branch length and secondary branching compared to the controls. PN90 PGE2F have decreased arborization closer to the soma, with increased secondary and tertiary branching compared to the controls. PGE2M and PGE2F have an overall decreased cross-sectional area of the soma at PN90 and increased likelihood of observing dendritic loops. Overall, this study demonstrates that maternal PGE2-exposure has sex and stage specific effects on hippocampal dendritic morphology in offspring.

P1-A-8: *Cortical layer 5 neurons form transient active circuits prior to thalamic innervation in the developing embryo*

Martin Munz[1], Arjun Bharioke[1], Georg Kosche[1], Cameron Cowan[2], Botond Roska[1]

[1]Institute of Molecular and Clinical Ophthalmology Basel, [2]IOB

Pyramidal to pyramidal neuron connections comprise a majority of the connections in cortical circuits, yet the assembly of these circuits remains poorly understood. Layer 5 pyramidal neurons are amongst the earliest born cortical neurons and show highly recurrent connectivity in the adult. Thus, they may form early pyramidal to pyramidal neuron circuits. Here, we show that embryonic layer 5 pyramidal neurons, identified through single cell transcriptomics, are active and show two phases of circuit assembly. Embryonic layer 5 pyramidal neurons already display three transcriptomic types, which correspond to the three adult layer 5 cell types. The first phase of circuit assembly, at E14.5, consists of transient two-layered circuits involving only neuron of the embryonic near projecting type, whereas the second, from E17.5 onwards, involves all three embryonic layer 5 types. Using two photon calcium imaging, visually guided patch clamp recordings, and pharmacology, all in vivo, as well as electron microscopy, we found that, in both phases, neurons display active somas and neurites, voltage-gated sodium conductances, and functional synapses. Additionally, from E14.5 onwards, we observed correlated activity between pairs of embryonic layer 5 neurons on all days, and, at E14.5, using acousto-optic two photon microscopy, these correlations were found between and within both layers.

Therefore, within the embryonic cortex, layer 5 pyramidal neurons form primordial active pyramidal to pyramidal neuron circuits, starting prior to thalamic innervation.

P1-A-9: *Differences in developmental fear processing in C57 mouse strains*

Hanista Premachandran[1], Kanza Naveed[1], Maithe Arruda-Carvalho[2]

[1]University of Toronto Scarborough, [2]University of Toronto, Scarborough

Fear processing is developmentally regulated in humans and rodents. Prior work suggests that rodents show developmental differences in the onset of persistent fear memories as well as in extinction learning. More specifically, rodents demonstrate an extinction switch from an immature and permanent extinction system towards an adult-typical and ineffective extinction system. Interestingly, fear processing differs between mouse strains in adulthood; however, no study to date has investigated strain differences in persistent fear memory or the extinction switch in early life. As such, the current study compares (1) persistent auditory fear memory and (2) the timing of the extinction switch in two C57 mouse lines (C57BL/6J from Jackson Laboratory, i.e. Jax mice, and C57BL/6NT from Taconic Biosciences, i.e. Taconic mice). We trained mice to associate a tone with a foot shock and either tested for 9-day retrieval (persistent fear), or extinguished the tone-shock association through repeated presentations of the tone alone and later tested for spontaneous recovery (e.g. the return of fear after the passage of time). We found that Taconic mice show earlier onset of persistent fear memory at postnatal day (P)18 compared to Jax mice at P21. Taconic mice also show an earlier onset of the extinction switch between postnatal day (P) 18-21, while Jax mice demonstrate the switch between P21-25. Delineating strain-specific timelines for fear processing in early life may signal corresponding changes in brain maturation, which could be leveraged to better understand brain development.

P1-A-10: *The involvement of PD-L2 in retinal axon guidance*

Xiaoyan Chen[1], Hidekiyo Harada[1], Philippe Monnier[1]

[1]University of Toronto

Axon guidance is an important process during embryonic development and is essential for synaptic activities in adulthood. Comprehending the mechanisms that regulate axon guidance and the development of neural circuit formation may help to find a cure for neural disorders and regenerate the nervous system. A previous study demonstrated that the Repulsive guidance molecule b (RGMb) is a guidance molecule which inhibits axon outgrowth in retinal ganglion cells (RGC) through the negative regulation in the Wnt pathway via the degradation of Wnt receptor Low-density lipoprotein

receptor-related protein 5 (LRP5). However, we could not confirm the direct interaction of RGMb and LRP5. Suggestive evidence shows the expression of Programmed cell death-1 ligand 2 (PD-L2) in the developing central nervous system (CNS) such as the retina and it is responsible for maintaining proper RGC numbers as a programmed cell death ligand. Yet, no study shows the role of PD-L2 in axon guidance. PD-L2 is also known to be the ligand of RGMb. In this study, we investigated the new function of PD-L2 in developing visual system and our data showed PD-L2 overexpression increased axon length in RGC primary culture. The axon length was suppressed by PD-L2 overexpression in RGMb/Wnt knockdown condition. These results imply a new function of PD-L2 and the potential interaction of PD-L2 with RGMb and Wnt signaling in the developing CNS.

P1-A-11: *Neighborhood disadvantage methylation score predicts risk for adolescent depressive symptoms*

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Growing up in disadvantaged environments is known to be an early adversity exposure that induces epigenetic modifications and increases the risk adult psychiatric diseases. However, there are important individual differences, not all the children exposed to adversity will develop psychopathology in the long term. To identify markers of risk, we used effect sizes described in an epigenetic wide association study (EWAS, Reuben et al.,2021) to create a methylation score associated with Neighborhood Disadvantage (ND) in a large dataset (ALSPAC, N=841, 412 males, samples collected at age 7). We then investigated the association between ND methylation score and adolescent depression (ICD-10 diagnoses at 17 years of age). Logistic regression adjusting by sex and blood cell count shows that higher methylation scores (representing epigenetic alterations linked to being raised in more disadvantaged neighborhoods) are associated with increased odds of depression at 17 years of age (OR=1.534, p=0.021]. Enrichment analysis of the genes associated with the CpGs that compose the score revealed that these genes are related Notch signaling, that plays a prominent role in the formation and function of the nervous system. These findings may suggest that the ND methylation score holds potential as a biomarker in identifying children at high risk for adolescent depression and highlight the importance of a supportive social environment in buffering the impact of adversity on brain function.

P1-A-12: *Capicua is required for the regulation of adult hippocampal neurogenesis*

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Adult hippocampal neurogenesis (AHN) is the cellular pathway from neural progenitor cells (NPCs) to adult-born neurons in the adult hippocampus. AHN is important for proper learning, memory, cognition, and mood function but is severely decreased in adult-onset memory and mood disorders. Understanding the biological intricates that regulate AHN may lead to treatments for learning and memory loss. The cellular stages of AHN involve NPC proliferation and differentiation, followed by neuron maturation. These stages are regulated by specific temporal expression of selective transcription factors. We found that the transcriptional repressor capicua (CIC) is expressed in NPCs but becomes downregulated during NPC differentiation. This is followed by a substantial upregulation during neuron maturation. Such expression changes suggest CIC may play a role in AHN. Here we find that deleting CIC in the mouse hippocampus, including the adult hippocampal neuronal lineage, leads to reduced total NPCs, resulting from increased progenitor differentiation into immature neurons. Furthermore, immature neurons in the mutant mice had impaired dendrite complexity, abnormal migration, and delayed progression to fully mature granule neurons. Together, our results show that CIC plays a critical role in NPC differentiation and neuronal maturation in AHN. Our study reveals a previously unrecognized role for CIC in AHN. Further investigations into the genes and pathways that CIC regulates may reveal crucial molecular inroads and therapeutic entry points into adult-onset memory and mood disorders.

P1-A-13: *Selective engagement of synaptic coupling using tACS*

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Transcranial Electrical Stimulation (TES) and transcranial magnetic stimulation (TMS) are promising non-invasive treatments for neurological and neuropsychiatric disorders. Although amplified interest and reports about their effectiveness, little is known about the way they engage and interfere with both individual and populations of neurons, and generally how TES engages brain plasticity. Ubiquitous neural diversity and heterogeneity, related to morphology, function, and intrinsic cellular features, result in widely distinctive responses to stimuli, and thus may well influence the effectiveness of therapeutic approaches that pertain to plasticity. As a first approach to this problem, we study the effect of tACS on individual and coupled neurons. Based on a leaky integrate and fire neuron model, we use the Hebbian STDP rule to reflect plastic changes in network connectivity. Focusing on the asynchronous regime, we explored the response of both individual cells and populations to periodic stimulation of varying intensities and frequencies - and how such responses were impacted by heterogeneity. Stimulation response depends on the incoming stimulation frequency and membrane

time constant. However, stimulating two neurons that are coupled bidirectionally with chemical synapses, different time constants enable stimulation to selectively potentiate synapses from a neuron with a lower time constant (faster and more responsive to the stimulation) to the neuron with a higher time constant (slower) using adequately tuned stimuli. This effect can alter the structural connectivity of the neural network, providing important insight into how to use TES to influence plasticity and stabilize stimulation-induced changes in brain connectivity.

P1-A-14: *Full-neuron in vivo imaging reveals activity dependent patterned remodeling of dendritic inputs*

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How developing brain neurons direct dendritic arbor growth and synaptogenesis to optimize encoding properties is poorly understood, yet central to understanding formation of functional circuits, or the dysfunctional structures underlying common neurodevelopmental disorders. In order to investigate the role of sensory experience in directing neuronal growth and connectivity in the awake developing brain, we have developed a custom random-access two-photon microscope capable of capturing full dendritic arbor structural growth and activity. We employ genetically-encoded fluorescent biosensors of glutamate to capture presynaptic activity, and calcium indicators to capture postsynaptic responses and action potentials. By providing controlled plasticity-inducing visual stimuli while recoding morphological changes and activity from individual growing tectal neurons in the developing brains of Xenopus laevis tadpoles we are able to directly link structural and functional plasticity. Results reveal rules of growth and synaptogenesis that direct experience-driven improvement in encoding.

P1-A-15: *Impact of early life stress on serotonin neuron activity and behaviour*

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Serotonin is a neurotransmitter that plays an important role in neurophysiological processes. Serotonin neurons innervate brain-wide regions that are involved in regulating emotion and behavior. Alterations in serotonin levels during critical brain developmental periods are associated with long-term changes in emotional regulation. Yet, the mechanisms underlying this association remain to be determined. Using a mouse model of chronic developmental stress, we aim to determine how early life stress (ELS) impacts brain-wide serotonin activity and consequent behaviors. We use the limited

bedding and nesting (LBN) model during the first postnatal week of life (postnatal days 2-9). Upon adolescence, we observe social behaviors in the home-cages of control and ELS mice until adulthood. Upon adulthood, we perform a standardized behavioral test battery to assess social, anxiety-like, depressive-like, and acute stress response behaviors. Using the Pet1cre-Ai148 transgenic mouse line, we conduct in vivo calcium imaging via fiber photometry in mice expressing GCaMP6f specifically in serotonin neurons to visualize neuronal activity during behavioral testing. Finally, we perform immunohistochemistry (IHC) on collected brain tissue and analyze for markers of neuronal activation (cFos). Preliminary data show some adulthood behavioral sex differences between control and ELS conditions. In-progress work includes analyzing fiber photometry and IHC data. Overall, our project will contribute to understanding the impact of ELS on serotonin neuron activity and long-term behavioral consequences.

P1-A-16: *The role of mcl-1 in developmental neurogenesis*

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Introduction: Neurogenesis is marked by neural precursor cells (NPCs) exiting the cell cycle and differentiating into neurons. Changes in mitochondrial morphology regulates neurogenesis through mediating a metabolic switch from glycolysis to oxidative phosphorylation (OXPHOS). Myeloid cell leukemia 1 (Mcl-1), a B-cell lymphoma 2 family member, is essential for survival of NPCs during neurogenesis. A distinct isoform of Mcl-1 on the mitochondrial matrix (Mcl-1matrix) regulates mitochondrial dynamics. It remains elusive whether Mcl-1 affects mitochondrial dynamics during neurogenesis. This leads to my hypothesis that Mcl-1 promotes the transition from glycolysis to OXPHOS through mediating mitochondrial fission-fusion dynamics during neurogenesis. Methods: Mcl-1 conditional knockout (MKO) mouse lines were generated using the Cre/Lox system. The effect of Mcl-1on cell cycle exit in the developing forebrain was determined through a BrdU/EdU pulse assay. Mitochondrial number and morphology in MKO embryos was examined through immunohistochemistry (IHC) with NanoJ SRRF processing and electron microscopy (EM). Results: In the MKO, significantly more NPCs exited the cell cycle at E11. IHC and EM analysis revealed that mitochondria were smaller and more numerous in MKO NPCs consistent with differentiation. Conclusion: These results suggest that Mcl-1 promotes neurogenesis by inhibiting mitochondrial fission in NPCs. Further studies are necessary to identify which Mcl-1 isoform exhibits this function and its potential effect on cellular respiration. Funding: Memorial University Faculty of Medicine Dean's Fellowship - S.C. Discovery grant from the Natural Sciences and Engineering Research Council of Canada - J.V.

P1-A-17: *Store-operated calcium entry promotes phosphorylation of transcription factor CREB and gene transcription in a human neural progenitor model*

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Calcium (Ca2+) is an abundant second messenger that is sequestered in the endoplasmic reticulum (ER) until it is needed. The ER Ca2+ store is tightly regulated by store-operated Ca2+ entry (SOCE)--a mechanism that promotes a distinct Ca2+ influx through ORAI channels when the ER is depleted. Recent evidence suggests that SOCE is important for regulating self-renewal, migration, and differentiation of neural progenitor cells (NPCs), which are the progenitor cells that give rise to glial and neuronal cell types populating the central nervous system during development. A transcription factor that plays a role in neurogenic processes is cAMP Response Element-Binding Protein (CREB). Although both SOCE and CREB have been separately found to participate in various aspects of neurogenesis, and that CREB is well known to be regulated by Ca2+-sensitive pathways, no direct connection has been made between them in NPCs. So, we sought to explore a link between SOCE-specific Ca2+ influx to CREB activation and downstream transcription of neurodevelopmental genes using human induced pluripotent stem cell (iPSC)-derived NPCs. We show here that activation of SOCE results in increased CREB phosphorylation at serine 133. Intriguingly, this event appears to be separate from the known CREB-activating pathways: PKA, ERK, CAMKII, or AKT. To better understand the effect that CREB phosphorylation can have on transcription, we also performed an RNA-Seq analysis. Overall, our efforts support a deeper investigation of SOCE-dependent CREB activation and the signalling cascades it regulates in NPCs.

P1-A-18: *Etv5 is not required for Schwann cell development but is required to regulate the Schwann cell response to peripheral nerve injury*

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Schwann cells are the principal glial cells of the peripheral nervous system, and their development into myelinating glia is critically dependent on MEK/ERK signaling. Ets transcription factors, including Etv5 are downstream effectors of the MEK/ERK pathway. In our initial study, we analysed Etv5tm1Kmm knockout mice with exons 2-5 deleted (designated Etv5-/-). We performed analyses at embryonic days (E) 12.5, E15.5 and E18.5, focusing on Schwann cells in the dorsal root ganglia (DRG).

Throughout embryogenesis, markers of satellite glia (glutamine synthetase) and Schwann cells, including TFs (Sox10, Sox9, Tfap2a, Pou3f1) and non-TFs (Ngfr, BFABP, GFAP), were expressed similarly in wild-type and Etv5-/- DRGs. Furthermore, by performing cell counts at E18.5, similar numbers of Sox10+ Schwann cells and NeuN+ neurons were generated the Etv5-/- DRG, suggesting no gross developmental defects were detectable. We next performed peripheral nerve injuries at postnatal day (P) 21, revealing that Etv5-/- mice had an enhanced injury response, generating more Sox10+ Schwann cells compared to wild-type animals at five days post-injury. Thus, while Etv5 is not required for Schwann cell development, possibly due to redundancy with Etv1 and/or Etv4, Etv5 is an essential negative regulator of the peripheral nerve injury repair response. We are now confirming these findings using an Etv5 conditional knock-out (cKO) approach using a Sox10-Cre driver to delete exons 10-11, generating a true null, and determining whether an increased numbers of Schwann cells would lead to better regenerative success using behavioural assays measuring motor recovery.

1B. Neural Excitability, Synapses, and Glia: Cellular Mechanisms

P1-B-19: *Reduced but not diminished: single-compartment oriens lacunosum-moleculare (OLM) cell model captures detailed model behaviour and explains theta resonance in OLM cells*

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Conductance-based models have played an important role in the development of modern neuroscience. Mathematical models are powerful "tools" that enable theoretical explorations in experimentally untenable situations. With advances in cell imaging and computational power, multi-compartment models with morphological accuracy are becoming common practice. However, as much as details increase the biophysical accuracy, they also muddle interpretability. Thus, model reduction is necessary to find the balance between biophysical fidelity and understanding. We use our developed state-of-art multi-compartment OLM cell model and reduce it to a single compartment model via "biophysical preservation constraints", and using current injection data as a basis for comparison. We examine the biophysical fidelity of the reduced model by comparing analyses using it with those done using the full, multi-compartment model. We find that our reduced model produces results that are comparable to that of the full model. That is, it can capture both in vitro and in vivo complex behaviours of the original model as well as a theta frequency (~3-12 Hz) spiking resonance, a defining feature of the OLM cell type. We then use the reduced model to show that hyperpolarization-activated inward channels could be responsible for preference to theta resonant frequencies. In addition to further analyses to decipher the interacting biophysical dynamics, this

reduced model could be used as a template to interface with experimental recordings for direct parameter estimation of biophysical characteristics.

P1-B-20: *Negative regulation of Arc transcription via eRNA and Brd4 interaction*

Alicyia Walczyk-Mooradally[1], Cara Aitchison[1], Begum Alural[1], Tristen Hewitt[1], Jasmin Lalonde[1]

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Activity-induced DNA double-strand breaks (DSBs) in the promoter region of neuronal immediate-early genes (IEGs) have been found to facilitate fast transcription initiation by overcoming genomic topological constraints. Since DNA DSBs can interfere with cell survival, non-homologous end joining (NHEJ) repair is also thought to play a role in this event. An intriguing observation from our group suggests that reduced bromodomain-containing protein (Brd4) level results in higher BDNF-induced expression of the IEG Arc. Considering that Brd4 can recruit NHEJ proteins to DNA DSBs, we hypothesized that enhancer RNAs (eRNAs) produced at the Arc distal promoter guide a Brd4 protein complex to repair DNA damages and end transcription. Supporting this model, we first confirmed that reduced activity of Brd4 in mouse primary cortical neurons results in increased Arc mRNA production after 6-hour BDNF stimulation. Next, we use biochemical and imaging techniques to demonstrate DNA DSBs resulting from BDNF signaling, including localized events within the Arc promoter. Also, we show that Arc eRNAs are simultaneously produced. Lastly, we provide evidence for the interaction between Arc eRNAs and Brd4. Conclusively, our results indicate that Arc promoter regions are cleaved by Topoisomerase IIβ to facilitate rapid transcription, and that BDNF-induced eRNA production interacts with Brd4 to effectively end transcription. Our findings provide new insight into the neuronal role of eRNAs and may help further our understanding of the genomic complexity underlying the mechanisms of learning and memory.

P1-B-21: *Downregulation of choline acetyltransferase induces neurite outgrowth in adult sensory neurons*

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The enzyme choline acetyltransferase (ChAT) catalyzes the biosynthesis of the neurotransmitter acetylcholine, an agonist of muscarinic acetylcholine type 1 receptor (M1R) that regulates neurite outgrowth in sensory neurons. However, the regulatory role of ChAT in sensory neurite outgrowth remains elusive. Here we report that the ChAT mRNA level was significantly upregulated after 48h in dissociated adult rat dorsal root ganglion (DRG) neurons following treatment with a cocktail of

neurotrophic factors (1 ng/ml NGF, 10ng/ml NT-3, and 10ng/ml GDNF) compared to control. Immunostaining studies show ChAT expression in ~70% of DRG neurons, and by utilizing a fluorescent dye ATTO590-labeled muscarinic toxin 7, a specific negative allosteric modulator of M1R, we confirmed the presence of M1R in ~50% of ChAT +ve neurons. In cultured DRG neurons, knocking down ChAT mRNA using neuron-specific adeno-associated virus AAVPHP.S, which delivered ChAT-shRNA, significantly increased neurite outgrowth compared to scrambled-shRNA. In contrast, AAVPHP.S-delivered ChAT-shRNA exerts no additional effect on neurite outgrowth in neurons lacking M1R when compared with wild-type controls. Thus, these findings illustrate that downregulation of ChAT expression is sufficient to enhance neurite extension in vitro and thereby unveil a previously unappreciated neurite outgrowth modulatory effect of ChAT in DRG neurons. This data clarifies the mechanisms of cholinergic constraint on neurite outgrowth and will enable the development of novel therapeutics for peripheral neuropathy. Funding: CIHR# PJT-162172.

P1-B-22: *Properties of activity-dependent spinogenesis in the developing and adult hippocampus*

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Growth of new synapses in the hippocampus is thought to contribute to neural circuit rewiring during memory formation. However, the properties and age-dependence of new synapse formation at the single synapse level remain poorly defined. We used 2-photon imaging and photolysis of caged glutamate to investigate de novo formation of individual dendritic spines in acute hippocampal slices from developing and adult mice. Photostimulation of CA1 dendrites with 40 uncaging pulses at 5 Hz elicited spinogenesis in 30% of trials in developing mice (P7-21). The success rate of this was age-dependent, dropping off after P14. Spinogenesis failed to occur by P21 and in adult mice. It was also dependent on dendritic branch order as it occurred more frequently in primary dendrites. Increasing the intensity of dendritic photostimulation significantly enhanced the rate of spinogenesis in young mice, as did priming with induction of structural long-term potentiation (sLTP) at a nearby spine prior to dendritic activation. Neither of these methods affected the inability to elicit spinogenesis in adult slices. These findings provide better understanding of the properties of de novo spinogenesis in the hippocampus and highlight that it is readily inducible during development but not in adulthood. Because strong evidence exists for in vivo learning-induced synapse formation in mature animals, ongoing experiments are aimed at determining the activity patterns and mechanisms that enable spinogenesis to occur in the adult hippocampus.

P1-B-23: *GAD and EAAT4 protein expression are regulated by nNOS in the murine cerebellum across development and between sexes.*

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Introduction: Cerebellar ataxia is a neurodegenerative disorder characterized by uncoordinated muscle movement that is inherited or arises from traumatic brain injury and has no cure. The cerebellum consists of Purkinje neurons (PNs) that comprise the sole GABAergic output from the cerebellum, and parallel fibers (PFs) that produce high levels of nitric oxide (NO) from the activity of neuronal nitric oxide synthase (nNOS). Previous studies demonstrate that nNOS/NO signaling is crucial for regulating PF-PN synaptic transmission hence cerebellar functions. However, a study has yet to characterize the effects of NO on specific PN functions such as glutamate uptake through excitatory amino acid transporter 4 (EAAT4) and GABA production through glutamic acid decarboxylase (GAD). This study aims to examine whether nNOS/NO signaling regulates EAAT4 and GAD expression/function between sexes in PNs by using wildtype (WT) and nNOS-/- mice. Hypothesis: EAAT4 and GAD protein expression and function is altered in nNOS-/- mice throughout development and between sexes. Material and Methods: Cerebella were collected from male and female WT and nNOS-/- mice at postnatal days 3, 7, 14, and 49 and prepared for immunohistochemistry and immunoblotting to visualize EAAT4 and GAD. A GABA ELISA was used to determine GAD function in PNs. Results: EAAT4 and GAD expressions were lower in males compared to females in nNOS-/- mice across timepoints. Conclusion: NO signaling is essential in regulating EAAT4 and GAD expression/function in PNs. Importantly, results from this study may lead to advancements in treating ataxia.

P1-B-24: *The location dependence of NMDA receptors in synaptic plasticity*

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Due to a dual need for pre- and postsynaptic activity, postsynaptic NMDA receptors (NMDARs) are thought of as coincidence detectors in Hebbian plasticity. However, there are also presynaptic NMDARs, which due to their location cannot serve this function, so we explored what they do. We previously found that presynaptic NMDARs in mouse visual cortex (V1) layer-5 (L5) pyramidal cell (PC) control synaptic release. Here, we investigate the roles of pre- and postsynaptic NMDARs in V1 L5 PC synaptic plasticity. To delete NMDARs in all V1 PCs, we created the triple transgenic mouse Emx1Cre/+;Ai9tdTom/+;NR1flox/flox (3TG). For sparse NMDAR deletion, we injected AAV9-eSYN-mCherry-iCre-WPRE in V1 of NR1flox/flox mice. Using MNI-NMDA uncaging in P11-18 acute slices, we verified that postsynaptic NMDARs were deleted in PCs of 3TG (0.020 ± 0.5 pA, n = 31 vs. control -48 ± 6 pA, n=19; $p < 0.001$) and viral NMDAR deletion animals (0.27 ± 0.6 pA, n = 5 vs. control 40 ± 12 pA, n = 5; $p < 0.05$). Furthermore, AP5 wash-in did not decrease mEPSC frequency in 3TG deletion mice (92%

± 4%, n = 18 vs. control 60% ± 12%, n = 5; $p < 0.05$), consistent with presynaptic NMDAR deletion. In 3TG NMDAR deletion animals, L5 PC basal dendrite spine density was reduced (2.5 ± 0.2 spines/10 µm, n =29; vs. 3.8 ± 0.2 spines/10 µm, $p < 0.001$), suggesting that NMDARs generally promote synapse formation and/or stability. Next, we will use paired recordings in sparse NMDAR deletion mice to explore how pre- and postsynaptic NMDARs differentially influence short and long-term synaptic plasticity.

P1-B-25: *Developing a human iPSC-based co-culture system to investigate how microglia regulate the development of neural network connectivity.*

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Neurons generate excess number of synapses during early brain development, called synaptogenesis. To establish a mature and functional network, our brains need to eliminate excess synapses according to their signal strength. Microglia, the brain's resident macrophages, participate in both synaptogenesis and synaptic pruning. Aberrant microglial clearance of synapses is associated with severe neurological disorders, like schizophrenia and Alzheimer's disease. However, incomplete representation of human disease in animal models and relatively rare sources of human tissue samples hinder therapeutic drug development. Therefore, I built a human induced pluripotent stem cell (iPSC)-based co-culture system, which contains both neural cells and microglia. To investigate how microglia regulate the development of neural network, I combined traditional molecular and immunostaining assays with the Multi-Electrode Array (MEA) technology to characterize synaptogenesis and synaptic elimination in my co-cultures. I also designed a fluorescence protein-based imaging tool in the co-culture system, which can help visualize synapses in real-time, providing a fast and efficient strategy for screening assays. Finally, to investigate the molecular mechanism regulating synaptic elimination, I developed complement component C1QA knockout cell lines using CRISPR and differentiated C1QA knockout microglia to build co-cultures. My system will significantly extend the toolbox to study human-specific features during normal brain development and in pathological situations.

P1-B-26: *Postnatal choline supplementation ameliorates deficits in hippocampal synaptic plasticity following prenatal ethanol exposure*

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Ethanol exposure is teratogenic to the developing hippocampus and results in a range of cognitive impairments known as Fetal Alcohol Spectrum Disorders (FASD). Prenatal ethanol exposure (PNEE) in rodent models produces reliable deficits in long-term potentiation (LTP) in male offspring that correlate to deficits in learning and memory. Female PNEE offspring, however, do not have consistent impairments in LTP. Currently there is no treatment to improve hippocampal function following PNEE, but work is underway exploring the use of the nutrient choline. The objective of this study was to explore whether choline supplementation could improve hippocampal LTP in PNEE offspring. Methods: Sprague Dawley rats were administered an ethanol-containing diet from gestational day 1-22. Offspring were treated with choline chloride from postnatal day (P) 10-30 and used for in vitro electrophysiology experiments from P31-35. LTP was induced in the dentate gyrus using high frequency stimulation. Results: Male PNEE offspring had a robust increase in LTP with choline treatment. Female offspring did not have deficits in LTP following PNEE; possibly could be due to a compensatory hyperexcitability. Choline treatment returned excitability in PNEE female offspring to control levels. PNEE and choline treatment did not significantly alter LTP in adulthood, but alterations in plasticity may be evident using subthreshold conditioning stimuli. Conclusions: These data demonstrate that choline treatment may be a beneficial treatment for FASD by improving hippocampal synaptic plasticity.

P1-B-27: *GM1 ganglioside alleviates LPS and amyloid mediated microglial inflammation by increasing autophagy flux*

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Gangliosides are glycosphingolipids highly enriched in the central nervous system, making up 10% of total lipid content. They play a critical role in signaling on the cell membrane. Ganglioside dysregulation has been observed in neurodegenerative diseases, such as Alzheimer's Disease (AD). In AD, microglia phagocytose and degrade beta-amyloid (Aβ) deposits in the brain, but chronic activation leads to neuroinflammation and AD exacerbation. GM1 ganglioside is known to exert an anti-inflammatory effect. This study investigates the anti-inflammatory mechanism of GM1 on modulating the autophagy pathway in microglia. Methods: BV2 microglia were treated with LPS and Aβ. Autophagy modulation was achieved with the mTOR inhibitor rapamycin and GM1. Inflammation was measured by gene expression of cytokines and ganglioside enzymes. Autophagy was measured by p62 and LC3 expression. Ganglioside levels were detected by electrospray-ionization mass spectrometry. Result: LPS and Aβ treatment increased pro-inflammatory cytokines in microglia and promoted ganglioside degradation enzyme expression. Elevated inflammation corresponded with suppressed autophagy. GM1 pre-treatment prior to LPS and Aβ blunted the inflammatory response and restored autophagy flux, comparable to rapamycin, through autophagy initiation. Conclusion:

GM1 alleviated the microglia inflammatory response by driving the autophagy pathway. Further investigation is required to link autophagy flux with lysosomal clearance. GM1 upregulation of autophagy may be a potential therapeutic target to resolve neuroinflammation in AD.

P1-B-28: *Involvement of hippocampal astrocytic connexin-43 in morphine dependence*

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Repeated exposure to drugs of abuse can lead to dysregulation of chemical synapses by altering the release and uptake of neurotransmitters. Such alteration in neurotransmission modify synaptic plasticity which cause addictive-like behaviour. Our previous study shed light on the involvement of glial cell in morphine induced behavioural responses . It has been shown that glial cells play an indispensable role in synaptic transmission through the release of gliotransmitters into and uptake of neurotransmitters from the synaptic cleft. Connexin-43(Cx43), the dominant Cx protein in astrocytes, is the main component of astrocytic gap junctions and hemmichannels. It has a critical role in synaptic efficacy through setting the amount of presynaptic gliotransmitter release in physiological conditions. It is probable that addictive substances affecting gliotransmitters release through the alteration of Cx43 function. In this study, we examined the role of the hippocampal-specific astrocytic connexin (Cx43) in morphine-induced behavioral responses. Male rats received subcutaneous (s.c.) morphine sulfate (10 mg/kg) at an interval of 12 h for 9 days. The animals received microinjection of TAT-Gap19 (inhibitor of Cx43) into the CA1 region before each morning morphine administration. The animals were assessed for morphine dependence by monitoring naloxone hydrochloride precipitated withdrawal somatic signs.Results showed that animals receiving TAT-Gap19 before morphine injection demonstrated a significant reduction in several signs of morphine withdrawal Our findings suggest that hippocampal Cx43 may be involved in morphine-induced behavioral responses. Therefore, gliotransmitter release by astrocytes seems to be a mechanism which is engaged in addictive-like behaviors.

P1-B-29: *Observing in-vivo claustrum activity during sleep using two photon microscopy*

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The claustrum is a small subcortical nucleus that has been recently implicated in sleep, but there has been conflicting data about when and how the claustrum is active across waking and sleep states in the mouse. The claustrum's thin, sheet-like shape and depth in the brain have stymied conventional

techniques to observe claustrum activity in-vivo. To overcome these technical limitations, we have combined virally mediated, pathway specific expression of jGCaMP8m with in-vivo thin-skull two-photon imaging of claustrum axons during waking, slow wave sleep, and rapid eye movement sleep. With this methodology, we present a characterization of cell specific retrosplenial-cortex-projecting claustrum neuron activity through the sleep-wake cycle. Preliminary data suggests the CLA-RSP pathway is most active during slow wave sleep and quiet awake states, while rapid eye movement sleep exhibits an almost complete silencing of claustrum activity. These data suggest the claustrum exerts its influence over the cortex most predominantly during slow-wave brain states.

P1-B-30: *Selective inhibition of astrocytic connexin43 gap junctions prevents the induction of long-term potentiation in the spinal cord dorsal horn by disrupting the release of lactate*

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The long-term potentiation (LTP) of synaptic connections located in the spinal cord dorsal horn is closely associated with the development of pathological pain. Recent studies have demonstrated the importance of astrocytes in neurotransmission and synaptic plasticity. These glial cells form vast intercellular networks that provide neurons with metabolic support necessary to sustain their high energy demands. Individual astrocytes are connected to one another via connexin43 (Cx43) gap junctions, which mediate the direct exchange of ions, second messengers and other small molecules between coupled cells. In this study, we test the hypothesis that inhibition of astrocytic gap junctions will lead to impaired dorsal horn LTP, as a result of diminished support for neurons. Using electrophysiology, neuronal excitability was measured via the recording of postsynaptic field potentials (fPSPs) in spinal cord explants from adult mice; low frequency stimulation (LFS) was then applied in order to produce dorsal horn LTP. In the control group, LFS induces the potentiation of spinal pain pathways to 125% baseline. Inhibition of Cx43 gap junctions using the Gap27 peptide prevents the development of spinal LTP, as fPSPs remain at 96% baseline. However, exogenous administration of lactate -an energy substrate- partially reverses the effect of Gap27 on synaptic strength (112% baseline). Our results indicate that pharmacological blockade of Cx43 gap junctions disrupts lactate shuttling from astrocytes to neurons, which is necessary for the development of LTP in the dorsal horn.

P1-B-31: *Disruption of the autism-associated gene SCN2A differentially alters synaptic development and bioenergetic signaling in patient iPSC-glutamatergic neurons*

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SCN2A is an autism spectrum disorder (ASD) risk gene and encodes a voltage-gated sodium channel, NaV1.2. Autism-associated SCN2A variants are thought to be pathogenic by reducing channel function; however, the impacts of autism-associated SCN2A de novo variants on human neuron development are unknown. We studied NaV1.2 function using isogenic SCN2A-/- induced pluripotent stem cells (iPSCs), and patient-derived iPSCs harboring a p.R607* or a C-terminal p.G1744* de novo truncating variant. We generated excitatory glutamatergic neurons and found that SCN2A+/p.R607* and SCN2A-/- neurons displayed a reduction in synapse formation and excitatory synaptic activity, suggesting loss-of-function phenotypes. However, the C-terminal p.G1744* variant, which leads to early-onset seizures in addition to ASD, altered action-potential dynamics but not synaptic activity. Further, proteomic analysis and functional validation of SCN2A+/p.R607* neurons revealed defects in bioenergetic signaling pathways, which were not present in SCN2A+/p.G1744* neurons. Our study reveals that autism-associated SCN2A de novo variants are not all loss-of-function, and differentially impact synaptic function and bioenergetic signaling.

P1-B-32: *The role of prefrontal cortex activity in the behavioural and synaptic effects of chronic stress*

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Major depressive disorder (MDD) is a devastating illness affecting 3.2 million Canadians, a number expected to increase following the COVID-19 pandemic. Current antidepressants are effective only in 50% of patients and take months to reach a therapeutic effect. Magnetic resonance imaging (MRI) and functional MRI studies consistently report impaired neural activity and lower volume of several brain regions, including the prefrontal cortex (PFC) in MDD patients. These changes are attributed to neuronal and synaptic atrophy. Since stress is a precipitating factor of MDD, chronic stress exposure is used to model behavioural and cellular features that resemble MDD in rodents, such as increased anxiety, depressive-like behaviours and synaptic loss. In mice, we recently showed that chronic stress decreases PFC volume, and that PFC volume negatively correlated with behavioural deficits and positively correlated with synaptic density. However, the question remains whether these changes are linked to the neural activity of this brain region. In this study, combining cell-specific genetic and viral manipulations, we determine 1) if PFC hypo- or hyperactivity directly induces behavioural and synaptic

deficits and 2) we also examined if PFC hypoactivity exacerbates chronic stress effects. Considering the central role of the PFC in stress-related illnesses, this work will shed light on the direct contribution of PFC dysfunction to stress-induced behavioural and brain connectivity deficits, while determining which PFC deficits can predict susceptibility to stress.

P1-B-33: *Infection-induced inflammation and its relationship with cognitive decline and neurodegeneration in an aged mouse model*

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Microglia, brain resident macrophages, are important for maintenance of brain homeostasis and synaptic plasticity regulation, core processes for learning and memory. Aging, a risk factor for dementia and Alzheimer's disease, impairs microglial ability to maintain these functions and provide a proper response to threats. Our aim is to assess whether microglial dysregulation in aging is amplified by exposure to infectious stimuli, rendering individuals more vulnerable to cognitive decline or neurodegeneration-associated pathology. Further, the role of the aging gut, a major regulator of microglial functionality, will be investigated in this model using dietary modulation. To induce an immune response, 18-20-month-old C57BL6/J mice were systemically injected with the viral mimetic polyinosinic:polycytidylic acid. In a post-sickness phase, animals were tested for learning/memory using the open field, novel, and spatial object recognition tests, as well as Barnes maze. Plasma and feces were collected and processed for ELISA, metabolomics , and metagenomics, to analyze inflammatory/metabolic markers and characterize the intestinal microbiome features, respectively. Besides neurodegeneration markers, samples from the hippocampus, seat of learning and memory, were assessed for microglial density, morphology, and ultrastructure using advanced confocal and electron microscopy, as well as molecular profile with proteomics. Pre-treatment with ketogenic diet will be used to modulate aging-induced microglial vulnerability, hopefully improving cognitive scores with aging and/or infection.

P1-B-34: *Functional Characterization and Therapeutic Targeting of Pathogenic GABRA1 Variants Identified in Two Pediatric Patients with GABAAR Channelopathies*

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Mutations of GABAAR have reportedly led to epileptic encephalopathy and neurodevelopmental disorders. We first identified a novel de novo T292S missense variant of GABRA1 from a pediatric

patient with grievous global developmental delay, but no obvious epileptic activity. This mutation coincidentally occurs at the same residue as that of the previously reported GABRA1 variant T292I identified from a pediatric patient with severe epilepsy. The distinct phenotypes of these two patients prompted us to compare the impacts of the two mutants on the receptor function and search for suitable therapeutics. In this study, we used biochemical techniques and patch-clamp recordings in HEK293 cells overexpressing either the wild-type or the mutated rat recombinant GABAARs. We found that the α1T292S variant significantly increased GABA-evoked whole-cell currents, shifting the dose-response curve to the left without altering the maximal response. By contrast, the α1T292I variant significantly reduced GABA-evoked currents, shifting the dose-response curve to the right with a severely diminished maximum response. Importantly, we found that the T292S mutation-induced increase in GABAAR function could be fully normalized by the negative GABAAR modulator thiocolchicoside; whereas the T292I mutation-induced impairment of GABAAR function was largely rescued with a combination of the GABAAR positive modulators diazepam and verapamil. Our study demonstrated that α1T292 is a critical residue for controlling GABAAR channel gating, and mutations occurred at this residue may produce opposite impacts on the function of the receptors. Thus, the present work highlights the importance of functionally characterizing individual GABAAR mutations for ensuring precision medicine.

P1-B-35: *GPR120 agonism protects against LPS- and cytokine-induced microglia activation*

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GPR120 is a G protein-coupled receptor for long-chain fatty acids including omega-3 polyunsaturated fatty acids (n-3 PUFA) that are known to have beneficial effects on inflammation, metabolism and mood. GPR120 partly mediates the anti-inflammatory and insulin-sensitizing effects of n-3 PUFA in peripheral tissues, findings that are generating considerable interest in GPR120 as a therapeutic target. Despite these results, the contribution of brain GPR120 to neuroimmune responses and associated behavioral changes is still unclear. We found that GPR120 is highly expressed in mouse primary microglia and microglia isolated by fluorescent-activated cell from adult CX3CR1CreER-YFP mice. The aim of this study is to investigate the impact of GPR120 agonism (Compound A, CpdA) on microglial inflammatory response and sickness behaviors. In primary microglial cultures from whole brain, GPR120 agonism potently regulated LPS-induced pro-inflammatory mediator production and morphological change. ICV administration of CpdA alleviated hypolocomotion and anxiety-like behavior in LPS (and cytokine)-induced systemic inflammation. The nucleus accumbens (NAc) is a key structure to control emotion and motivation. Therefore, we targeted NAc microglia to examine how GPR120 agonism regulates cytokine-induced microglial activation. In NAc derived primary microglia, CpdA attenuated increased cytokines and microglial activator Iba1 mRNA expression after application

of cytokines. Morphological studies have also characterized CpdA's ability to inhibit microglial activation under neuroinflammatory duress.

P1-B-36: *Phylogenetic analysis of the in-vitro protein-protein interactions between the Presynaptic Scaffolding protein, Rab3 Interacting Molecule (RIM), and the extreme C-termini of the Voltage-gated Calcium Ion (CaV2) Channels*

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The primary role of CaV2 type voltage-gated calcium channels in driving neurotransmitter release at the presynaptic terminal is broadly conserved in animals. Genetic studies in vertebrates, fruit flies, and nematode worms reveal conserved protein-protein interactions that serve to localize CaV2 channels at the synapse active zone, enabling them to couple membrane excitation with Ca2+-dependent vesicle fusion. Specifically, the presynaptic scaffolding protein Rab3 Interacting Molecule (RIM), uses a PDZ domain to bind a conserved DDWC-COOH motif at the extreme C-terminus of CaV2 channels, tethering them close to docked synaptic vesicles. Outside of vertebrates, a direct physical interaction between CaV2 channels and RIM has not been tested or confirmed. Furthermore, the evolutionary origin of this interaction is unknown. Interestingly, animals possess two RIM paralogs: a known ortholog that regulates CaV2 channel trafficking (RIM-I), and a novel ortholog of unknown function (RIM-II). We find that CaV2 channel DDWC-COOH motifs are conserved in animals that share ancestry for synapse evolution but are absent in animals that lack synapses. The exception are ctenophores, which are argued to have independently evolved synapses, as they lack RIM-I and the canonical CaV2 channel DDWC-COOH motifs, instead only possess RIM-II and CaV2 channel SGDI-COOH motifs. Here, we are combining phylogenomics, protein biochemistry, structural analysis, and high-throughput screening to analyze the diversity of the RIM-CaV2 channel interaction, to understand its significance for synaptic evolution.

P1-B-37: *The Biophysical Characterization of an Acid-Sensing Ion Channel From Trichoplax adhaerens, an Animal Without a Nervous System*

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Acid-sensing ion channels (ASICs) belong to a diverse superfamily of ion channels known as degenerin/epithelial sodium channels (DEG/ENaCs). In mammalian nervous systems ASIC channels activate at low pH conditions and play numerous important roles including pain sensation, ischemia,

and learning and memory. ASICs are thought to be unique to a superphylum of animals known as deuterostomes, while in invertebrate animals, DEG/ENaCs evolved diverse gating modalities including mechanical gating in C.elegans and peptide gating in Molluscs. The earliest characterized DEG/ENaC channels belong to the cnidarian Hydra magnipapillata and were found to be insensitive to pH changes and directly activated by peptides. Our recent work has shown that uncharacterized DEG/ENaC homologs exist in even earlier diverging animal lineages: the Placozoans, Sponges and the Ctenophores. Trichoplax adhaerens belong to the Placozoan lineage and remarkably express nine DEG/ENaC homologs (TadNaCs2-10) that phylogenetically cluster with deuterostome ASICs. Using heterologous expression in CHO-K1 cells and whole-cell patch clamp electrophysiology we found that the TadNaC2 channel forms a functional channel with biophysical properties that highly resemble that of deuterostome ASICs. Upon acidification, the channel activates a bimodal current with an early calcium permeating transient current followed by a sodium-selective sustained current. Structurally, TadNaC2 retains the secondary structures found in DEG/ENaCs yet many of the key molecular determinants for proton activation of deuterostome ASIC channels are absent. However, mutagenesis analysis uncovered a unique set of residues for proton activation of TadNaC2, suggesting the independent evolution of ASIC channels in placozoans.

P1-B-38: *Exploration of the phylogenetic properties of the Na+ leak channel NALCN and its accessory subunits UNC-79, UNC-80 and Fam155A*

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The sodium leak channel NALCN plays a critical role in regulating the resting membrane potential of neurons and neuroendocrine cells. For proper function in vivo and in vitro, NALCN forms a complex with its accessory proteins UNC79 and UNC80, as well as the ER-resident protein FAM155. Previously, NALCN and FAM155 homologues were identified in yeast, suggesting an ancient association between these two channel subunits. However, yeast lack UNC79 and UNC80, and the evolutionary origins of these two subunits is unclear. Here, we corroborate reports that NALCN, UNC79, UNC80, and FAM155 homologues are present in every animal lineage except for ctenophores, proposed to be the most early-diverging animals. Unlike the related voltage-gated sodium and calcium channels which underwent significant genetic expansion in various lineages, NALCN and its subunits have generally remained as single copy genes. Interestingly, we find evidence for the emergence of the UNC80 subunit in Fungi, and of sequence homology between the UNC79 and UNC80 subunits. Altogether, these findings suggest that an ancestral UNC80 protein gave rise to UNC79 via gene duplication strictly in animals. In addition, in vitro expression of cloned NALCN subunits from humans and the early-diverging animal Trichoplax adhaerens reveal conserved regulation of NALCN channel protein expression by its co-expressed subunits. We also find that the subunits of voltage-gated calcium

channels, CaVβ and CaVα2δ, significantly boost NALCN protein expression in vitro, and are seeking to understand the significance of this observation.

P1-B-39: *Non-hyperglycemic media can support the metabolic needs of electrically active rodent primary neurons in long-term cultures*

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Neurons have a high metabolic demand met by a constant blood supply with glucose as the main energy substrate. We investigated if culture media with physiologic glucose levels supported the metabolic needs and sustained activity of primary neurons. E18 rat cortices were dissociated into single cells and plated in NeuroCult Neuronal Plating Medium supplemented with NeuroCult SM1 Neuronal Supplement (SM1) in 48-well microelectrode array (MEA) and Seahorse XF96 plates. On day 5, cultures were switched to either BrainPhys Neuronal Medium (BP) supplemented with SM1 [control] or BP with 15mM glucose supplemented with SM1 [BP(15)] by performing half-medium changes every 2 - 3 days. Media glucose levels were routinely measured using a YSI Biochemistry Analyzer. Spontaneous activity was recorded three times weekly on the MEA system for 8 weeks, and Seahorse ATP rate assays were performed on day 14 and 22. Neuronal activity in both media was comparable until the mean firing rate (MFR) of the control began to drop on day 14, decreasing to 0.7 ± 0.3 Hz by day 21 (mean ± SEM, n = 4). This coincided with a complete depletion of glucose not observed in BP(15). In contrast, BP(15) had a MFR of 2.9 ± 0.4 Hz on day 21, which rose to 4.0 ± 0.8 Hz by day 35 and was maintained until the end of the culture period (day 54). Additionally, ATP production in BP(15) was 45.7% higher than the control on day 21. These data indicate that BrainPhys Neuronal Medium supplemented with glucose at higher, but not hyperglycemic, levels can support the metabolic needs of active neurons in long-term culture.

P1-B-40: *Astroglial and neuronal calcium dynamics in response to stress in rodents*

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Astrocytes are ubiquitous brain cells that regulate synaptic transmission and neurotransmitter recycling through bidirectional interaction with neurons. Specifically, astrocytes respond to altered neuronal activity through changes in intracellular Ca2+ concentrations and release gliotransmitters,

which in turn act on neurons. Emerging research identify a critical role of astroglial dysfunctions in the major depressive disorder- and stress-related synaptic deficits. Thus, investigating changes in astroglial and concomitant neuronal Ca2+ transients in response to stress may help elucidate the astroglial involvement in depressive-like symptoms. In this study, neuronal and astrocytic Ca2+ transients were recorded using fiberphotometry in mice. Astroglial and neuronal specific adeno-associated viruses were infused in the prefrontal cortex to record Ca2+ transients using fiber optic cannula. We first investigated the changes in astroglial and neuronal Ca2+ mobilization baseline activity and reactivity to acute stress (tail pinch and immobilization stress). Further we also examined the effects of astroglial activation and neuronal inhibition using chemogenetics on neuronal and astroglial activity respectively, before and after acute stress exposure. Current studies are focusing on examining chronic stress effects on neuronal and astrocytic Ca2+ transients. This work will allow identification of cell activity alterations in response to stress and will shed light on the dynamic relationship between the astrocytic and/or neuronal dysfunctions associated with stress and depression.

P1-B-41: *Neurons release fatty acids by late endosome/lysosomal exocytosis*

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Fatty acids are essential for cell function, but their accumulation can be toxic. Fatty acid toxicity is an important yet understudied feature of several neurodegenerative disorders. To avoid fatty acid toxicity during oxidative stress, neurons release fatty acids that are then taken up and stored in glial lipid droplets. However, the mechanisms of neuronal fatty acid release are poorly understood. Here, using total internal reflection fluorescence microscopy, we show that cultured neurons exocytose fluorescently tagged fatty acids. We found that pharmacological stimulation of exocytosis decreased fatty acid accumulation in neurons and increased fatty acids released in the media and stored in glial lipid droplets. Conversely, knockdown of the machinery needed for late endosome/lysosome (LEL) exocytosis increased fatty acid accumulation in neurons and decreased fatty acids released in the media and stored in glial lipid droplets. Furthermore, knockdown of the LEL exocytosis machinery reduced glial lipid droplet formation in a Drosophila model of oxidative stress. Altogether, our study reveals LEL exocytosis as an important mechanism for fatty acid release from neurons that likely plays a key role in the pathophysiology of neurodegenerative diseases.

P1-B-42: *Rapid homeostatic modulation of excitatory synaptic transmission in the adult mouse hippocampus*

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Homeostatic synaptic plasticity (HSP) encompasses a suite of adaptive physiological processes that counteract age and disease-related neuronal perturbations. Yet, we lack a complete description of the homeostatic processes that operate within the mammalian brain. Here, we demonstrate a rapid homeostatic control of presynaptic neurotransmitter release in the adult hippocampus upon selective impairment of AMPA receptor-mediated neurotransmisson. This homeostatic mechanism can be induced within minutes and requires postsynaptic NMDAR function. The expression process includes evidence of substantial coordinated pre- and postsynaptic growth as determined by ultrastructural reconstruction of hippocampal volumes. Finally, selective induction of HSP at excitatory synapses by application of the allosteric glutamate receptor antagonists GYKI or perampanel induces a parallel potentiation of inhibitory transmission, a cross-modal effect that also requires postsynaptic NMDARs. The net effect, homeostatic restoration of excitation and potentiation of inhibition, is consistent with the anti-epileptic activity of perampanel, which is used to treat seizure in humans.

P1-B-43: *Schizophrenia-associated LRRTM1 regulates cognitive behavior through controlling synaptic function in the mediodorsal thalamus*

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Reduced activity of the mediodorsal thalamus (MD) and abnormal functional connectivity of the MD with the prefrontal cortex (PFC) cause cognitive deficits in schizophrenia. However, the molecular basis of MD hypofunction in schizophrenia is not known. Here, we identified leucine-rich-repeat transmembrane neuronal protein 1 (LRRTM1), a postsynaptic cell-adhesion molecule, as a key regulator of excitatory synaptic function and excitation-inhibition balance in the MD. LRRTM1 is strongly associated with schizophrenia and is highly expressed in the thalamus. Conditional deletion of Lrrtm1 in the MD in adult mice reduced excitatory synaptic function and caused a parallel reduction in the afferent synaptic activity of the PFC, which was reversed by the reintroduction of LRRTM1 in the MD. Our results indicate that chronic reduction of synaptic strength in the MD by targeted deletion of Lrrtm1 functionally disengages the MD from the PFC and may account for cognitive, social, and sensorimotor gating deficits, reminiscent of schizophrenia.

P1-B-44: *Stratum-specific role of LRRTM1 in regulation of long-term potentiation and dorsal CA1-associated behaviour*

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The hippocampus has a laminar organization with defined axonal inputs onto specific dendritic compartments of pyramidal neurons and granule cells. The characteristic laminar organization of the hippocampus is thought to be orchestrated in part by cell-surface synapse organizing proteins, some of which such as the leucine-rich-repeat transmembrane neuronal proteins (LRRTMs) are essential for mediating enduring changes in synaptic efficacy such as long-term potentiation (LTP). LTP is differentially expressed in the proximal and distal dendritic compartments of the CA1 pyramidal neurons constituting the stratum radiatum and stratum lacunosum moleculare respectively However, the molecular mechanisms underlying differential expression of LTP in the hippocampal laminae is poorly understood. We show here that LRRTM1 expression is largely restricted to the stratum radiatum. Loss of LRRTM1 in CA1 pyramidal neurons impaired LTP in the stratum radiatum but not in the stratum lacunosum moleculare. These deficits were corrected by the reintroduction of LRRTM1 or perfusion with a peptide that interferes with the endocytosis of GluA2-containing AMPA receptors. Our results further indicate that chronic reduction of synaptic strength in the dorsal CA1 by targeted deletion of Lrrtm1 in adult mice may account for memory deficits attributed to dorsal CA1.

P1-B-45: *BrainPalmSeq: A comprehensive RNA-seq database of palmitoylating and de-palmitoylating enzyme expression in the mouse brain*

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Protein palmitoylation is a reversible post translational lipid modification that can influence protein stability, trafficking and function. Dynamic S-palmitoylation is regulated by a large family of ZDHHC palmitoylating enzymes, their accessory proteins, and a small number of known de-palmitoylating enzymes. While cellular and regional coordination of gene expression is known to have a profound influence over enzyme-substrate interactions, the brain expression patterns of palmitoylating and de-palmitoylating enzymes have not yet been comprehensively explored. Here, we collated and analyzed expression data from publicly available bulk, pooled-cell and single-cell RNAseq mouse datasets for the known palmitoylating and de-palmitoylating enzymes, and their accessory proteins, to provide a comprehensive overview of their expression patterns in the mouse nervous system. We developed a

web-tool that enables interactive visualization of the expression patterns for these proteins in the nervous system (http://brainpalmseq.med.ubc.ca/), and explored this resource to find region and cell-type specific expression patterns that give insight into the function of palmitoylating and de-palmitoylating enzymes in the brain and neurological disorders. We found coordinated expression of ZDHHC enzymes with their accessory proteins, de-palmitoylating enzymes and other brain-expressed genes that included an enrichment of S-palmitoylation substrates. Finally, we utilized ZDHHC expression patterns to predict and validate palmitoylating enzyme-substrate interactions.

P1-B-46: *The role of the intellectual disability gene, Zdhhc9 in white matter development in the brain*

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Loss-of-function variants in the human Zdhhc9 gene are identified in 2% of patients diagnosed with X-linked intellectual disability. Clinical studies have shown regional changes in white matter content in the brains of patients with Zdhhc9 mutations, including reductions in overall white matter volume and altered microstructure of white matter tracts. In vivo research has shown that Zdhhc9 knockout (KO) mice exhibit similar reductions in corpus callosum (CC) volume. In this study we used bioinformatic analysis of publicly available RNA sequencing data and found that Zdhhc9 is highly expressed in the CC and oligodendrocytes and that loss of Zdhhc9 in vivo may impact myelin formation. Zdhhc9 expression is enriched in oligodendrocytes and is nearly two-fold higher in the CC than in any other region of the mouse brain. To unbiasedly assess how loss of Zdhhc9 affects the gene transcriptome of the CC, we performed RNA sequencing on the CC of Zdhhc9 KO mice. RNAseq results show differential expression of oligodendrocyte marker genes in KO mice, suggesting a decrease in mature oligodendrocytes in Zdhhc9 KO mice. Using electron microscopy to observe levels of myelination in the CC, we found a significant reduction in the percentage of axons that are myelinated in the Zdhhc9 KO CC. Additionally, immunostaining for Nodes of Ranvier shows a significant decrease in nodal density in the CC of Zdhhc9 KO mice. This work provides new perspectives into the role of Zdhhc9 in oligodendrocyte development and provides evidence that palmitoylation contributes to the development of white matter.

P1-B-47: *Ionotropic acetylcholine receptor dynamics control neuroendocrine cell activity*

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Underlying many behaviors, including motor execution, learning and neuroendocrine control, is a long-term change to neural activity following transient stimulation. The snail, Aplysia, engages in reproductive activity when brief synaptic input opens ionotropic acetylcholine receptors on neuroendocrine bag cell neurons, thereby causing a prolonged afterdischarge and egg-laying hormone secretion. The cholinergic depolarization is short-lived, but may recruit persistent Ca2+ current to sustain the firing. We used electrophysiology and fluorescent imaging of cultured bag cell neurons to examine how acetylcholine receptors can rapidly engage Ca2+ current, and then undergo protracted desensitization. Delivering wave-forms mimicking the acetylcholine-induced depolarization caused prolonged Ca2+ influx, as measured by whole-cell voltage-clamp or imaging of intracellular Ca2+, that was sensitive to Ca2+ channel blockers (Ni2+, Co2+ and Zn2+, but not Cd2+ or ω-conotoxin GIVa). Currents evoked by repeated pressure-ejections of acetylcholine exhibited near complete desensitization at ~3 min intervals, while at 10- to 120-min intervals, the remaining current was <60% of the first. When neurons were recorded from twice in the span of ~24 hours, by day 2, the current was >100% of the first, reminiscent of the ~18-hr refractory period presented by the afterdischarge in vivo. These results suggest that momentary cholinergic depolarization can elicit long-term change to activity, but is moderated by extended desensitization, potentially involving membrane trafficking of receptors.

P1-B-48: *Modular organization of quantal heterogeneity at a central synapse*

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<p>Functional synaptic heterogeneity is widely observed but poorly understood. We use the mature calyx of Held nerve terminal in mice as a model to address this question. The calyx contains main stalks with a varying number of bouton-like swellings which inversely correlate with release probability (Pr) of the whole terminal (Grande and Wang, 2011). Stalks contain large clusters of Ca2+ channels tightly coupled to synaptic vesicles (SVs) to support high Pr, whereas swellings contain small clusters of Ca2+ channels loosely coupled to SVs to yield low Pr (Fekete et al., 2019). Whether these different morphological modules with distinct Ca2+ channel topologies impacts unitary quantal release is not known. To address this issue, we examined miniature excitatory postsynaptic currents (mEPSCs) in morphologically diverse synapses and their Ca2+ dependence, complemented by analyses of the distribution of immunolabelled postsynaptic AMPARs relative to fluorescently tagged knock-in Ca2+ channels (Mark et al., 2011) in stalks and swellings. Preliminary data indicate that mEPSC amplitude inversely correlates with the number of swellings, where small clusters of Ca2+ channels are matched with small clusters of postsynaptic AMPARs. We propose that the same nerve terminal harbours modular constructs for distinct topographical arrangement of presynaptic Ca2+ channels and

postsynaptic AMPARs between low and high Pr sites, potentially underpinning the heterogeneity of quantal size at a central synapse. Supported by CIHR and NSERC

P1-B-49: *Context-dependent transcriptional regulation of microglial proliferation*

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Microglia, are the resident macrophages of the central nervous system (CNS), have several important functions which are essential for the normal development, maintenance, and homeostasis of the CNS. Disruption of microglia function is associated with multiple neurodegenerative and neurodevelopmental diseases. Both in a neurodevelopmental and neuropathological context, microglia proliferate massively. In the first case, their primary goal is to colonize the CNS and participate in its development. In the second case, microglia proliferate to protect the CNS and to maintain its homeostasis. Microglia proliferation requires finely orchestrated transcriptional regulation in order to appropriately coordinate the expression of several proliferation-related genes. We investigated and compared the transcriptional mechanisms associated with microglia proliferation in postnatal development and in an adult model of microglia depletion-repopulation. The data show that proliferating microglia induce the transcription of genes associated with the proliferation environment, as well as two groups of genes associated with proliferation. The first group of genes is already expressed in quiescent microglia and is regulated by the transcription factors Klf/Sp, Nfy and Ets. The second group represents genes that are newly induced upon entry into proliferation, and whose regulation involves the transcription factors Lin54 and E2f. Altogether we show that the transcriptional program associated with microglia proliferation is "context-dependent."

P1-B-50: *Implication of astrocytic glucocorticoid signaling pathway in the adaptive response to metabolic stress*

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In response to stress, glucocorticoids act via their specific glucocorticoid receptors (GRs) to induce metabolic and behavioral adaptation. This GR-dependent adaptation influences energy balance and feeding behavior, notably through the modulation of hypothalamic neuropeptide expression. Chronic

glucocorticoids exposure, however, contributes to the development of metabolic disorders that are commonly associated with behavioral deficits. Despite these data, little is known about cellular effectors of metabolic adaptation to stress, particularly in hypothalamic brain regions associated with metabolic regulation. Recent results suggest a relevant role of astrocytic GR activity in regulating the synaptic response to stress. We thus set out to test the hypothesis that astrocytes play a role in mediating adaptive metabolic processes in response to stress via GR activation. First, to evaluate metabolic stress impact on GR-expressing astrocytes plasticity in hypothalamus, we performed immunostaining for astrocytes and GR on mouse brain slices. Next, to directly implicate astrocytes in metabolic adaptation, we characterized the metabolic phenotype of wildtype and transgenic mice lacking GR specifically in astrocytes (GRfl/fl x Glast-Cre/ERT2) before and after metabolic challenge. This was followed by a battery of behavioural assays to determine whether targeting astrocytic GR signalling could rescue the anxio-depressive-like behaviours associated with metabolic distress. These results are a first step to a highlight of novel stress response mechanisms.

P1-B-51: *Insulin promotes RGC dendrite regeneration through ribosomal protein S6 kinase activation leading to restoration of neuronal function in glaucoma*

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We previously demonstrated that insulin promotes RGC dendrite regeneration through activation of the mTOR pathway. The precise mechanisms of insulin-mediated regeneration and role in vision restoration are unknown. Here, we asked: 1) what are the mTOR downstream effectors responsible for insulin-induced dendritic regrowth? 2) does insulin restore RGC function and visual responses in glaucoma? Ocular hypertension (OHT) was induced by injection of magnetic microbeads in Thy1-YFP mice. Daily insulin or saline eye drops started at 2-weeks after OHT induction and dendrites were reconstructed 1 week later. The role of the mTORC1 downstream effector, S6K, was assessed by loss of function using targeted siRNA. RGC survival and function were evaluated using quantification of RBPMS-positive neurons, single-RGC calcium dynamics using two-photon microscopy live imaging in transgenic mice carrying the calcium indicator GCaMP6f, and optomotor reflex assays. Insulin promoted a substantial increase in RGC dendritic length after OHT induction. S6K knockdown impaired insulin-mediated RGC dendrite regeneration. S6K increased mTORC2 activity through phosphorylation of SIN1. Insulin promoted robust RGC survival at 3 and 6 weeks of OHT relative to saline. Importantly, insulin restored light-evoked RGC calcium dynamics and improved visual acuity in glaucoma. Our data show that S6K is a key signaling component required for insulin-mediated RGC dendrite regeneration, an effect that is enhanced by crosstalk with mTORC2 through SIN1 activation. Importantly, insulin prevents RGC loss while restoring light-evoked responses and visual acuity. Our

data support a critical role for insulin as a pro-regenerative therapy and identify downstream targets to restore RGC connectivity and function in glaucoma

P1-B-52: *Multiscale investigation of the spatial selectivity of neurovascular coupling*

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Non-invasive functional brain imaging often relies on measuring vascular signals as surrogates for neuronal activity. However, the spatial dynamics of neurovascular coupling remains ill-defined in the cortex. Recent work has highlighted the contribution of proximal (1st-4th order) capillary pericytes to blood flow regulation, suggesting that spatial specificity could be achieved through fine control at the capillary level. Here, we aim to investigate the relationship between neurovascular coupling and neuronal activity across multiple scales. Simultaneous imaging of excitatory neuronal activity and vascular responses was performed through a cranial window, using two-photon microscopy, widefield fluorescence and intrinsic optical imaging. Imaging was performed in the mouse barrel cortex and neuronal activity was elicited by single whisker stimulations. At the mesoscale level, blood volume increases correlated well with excitatory neuronal activity, albeit with a higher point-spread function. Interestingly, at the microscopic scale, capillary responses were very heterogenous within a single whisker column, with some vessels exclusively responding to the associated whisker and others responding equally to the associated or neighbouring whisker. Capillary response heterogeneity could not be explained by differences in adjacent excitatory activity, which poorly predicted local capillary tuning. Rather, our results suggest that the mesoscopic spatial selectivity of hemodynamic responses results from a complex redistribution of flow within local capillary networks. These results suggest there is a functional resolution limit to hemodynamic measurements, where blood flow, at the single vessel level, may not reflect neuronal activity in its immediate vicinity.

P1-B-53: *Loss of Rai1 induces hippocampal hyperexcitability in mouse models of Smith-Magenis syndrome*

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Hyperexcitability of the brain circuits is a common feature of autism spectrum disorders (ASDs). Genetic deletion of retinoic acid induced 1 (RAI1) causes Smith-Magenis syndrome (SMS), a syndromic

ASD associated with intellectual disability, autistic features, maladaptive behaviors, overt seizures, and abnormal electroencephalogram (EEG). The mechanism underlying abnormal neuronal activity in SMS remains unknown. Here we show that deleting Rai1 from the glutamatergic but not gamma-aminobutyric acidergic (GABAergic) neurons results in increased seizure susceptibility in mice. Whole brain clearing and activity mapping pinpointed that the hippocampal dentate gyrus granule cells (dGCs) are consistently hyperactivated by chemoconvulsant administration or sensory experience upon Rai1 loss. Dentate gyrus gating impairment is associated with temporal lobe epilepsy. Rai1 deletion increased dGC neuronal population spikes ex vivo and prolonged time spent in seizure state in vivo. Glutamatergic Rai1 loss results in increased intrinsic dGC excitability in the absence of alterations in dGC spine density or dendritic morphology. Our work uncovers the mechanism of hyperexcitability in SMS by identifying Rai1 as a novel regulator of dGC intrinsic excitability.

1C. Disorders of the Nervous System

P1-C-54: *Initial clinical characterization, evolution and response to treatment in pediatric patients with multiple sclerosis. A 10-year case series*

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INTRODUCTION Pediatric multiple sclerosis (PMS) is a chronic, progressive demyelinating inflammatory disease of the central nervous system, accounting for 5.6% of all cases, the M:H ratio depends on the age of onset . Early diagnosis enables early initiation of DMT (disease-modifying therapy) and thus modifies the course of the clinical picture . Children have a more benign course but a higher relapse rate throughout their lives. MATERIAL AND METHODS This is a retrospective, cross-sectional, descriptive study of a series of pediatric cases with MS MS in the period from January 2009 to December 2019. Demographic, clinical and paraclinical data were collected as well as the clinical course by measuring the Kurtzke scale and annual relapse rate. Descriptive statistics were performed for demographic variables and non-parametric analysis for clinical and paraclinical variables due to the sample size. A database was created and SPSS version 25.0 was used for the corresponding analyses. RESULTS As for symptomatic symptoms, motor symptoms were present in 9/11 patients during the debut and throughout the relapses the number of patients presenting these signs of motor damage decreased, followed by sensory symptoms which followed the same pattern starting with 6/11, and in the third relapse only 2 cases presented them. The third syndrome in frequency was cerebellar with 7/8 patients and that was only present during the first and second relapse and finally visual and/or autonomic symptoms. The annual relapse rate of 11 patients followed for 5 years was on average 0.04 (0.016 to 0.08)

P1-C-55: *An actin-based 'tourniquet' provides neuroprotection following focal excitotoxicity at peripheral dendrites*

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During a stroke, disrupted regional blood flow creates an anoxic and nutrient-deficient core. Although we and others have determined the mechanism through which neurons in the core inevitably die, it remains unclear why neurons in neighbouring brain tissue (penumbra) have less predictable outcomes. Branches from penumbral neurons crossing into the core undergo a dramatic morphological change termed blebbing, forming "beads on a string", while the remainder of the neuron appears morphologically normal. As blebbing is associated with injured areas and observed throughout dead neurons, the dogma is that blebbing is pathological; however, it is reversible and occurs in response to stimuli below the threshold for cell death. Thus, we hypothesized that blebs are a form of intrinsic neuroprotection. We have created an in vitro model of the core-penumbra interface that targets isolated peripheral dendrites to allow interrogation of molecular mechanisms underlying blebbing. Here, we found that neurons sequester cytotoxic calcium in blebs of peripheral branches, preventing back-propagation towards the soma. They do this by forming a cytoskeletal tourniquet, proximal to blebs, allowing the otherwise healthy neuron to maintain function. When the tourniquet formation is disrupted, the neuron dies; yet, when maintained, the damaged branches either pinch off or recover, promoting cell survival. Taken together, this work is a step towards improving the penumbral viability and improving stroke outcomes.

P1-C-56: *MATR3 represses the inclusion of cryptic exons through binding transcripts using its RRM2 domain*

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MATR3 is an RNA binding protein implicated in amyotrophic lateral sclerosis (ALS) and neurodevelopmental diseases. MATR3 regulates alternative splicing and binds intronic regions flanking repressed exons. Previous studies implicate that MATR3 is involved in cryptic splicing. However, little is known regarding the role of MATR3 in cryptic splicing, the mechanism by which MATR3 regulates cryptic splicing, or how disease-associated mutations impact MATR3's splicing

function. Here, we show that loss of MATR3 leads to extensive cryptic splicing, while overexpression of MATR3 shows repression of cryptic splicing. Through rescue experiments with domain mutants of MATR3, we show that the RRM2 domain is required for cryptic exon repression. We demonstrate that MATR3 binds its splicing targets using its RRM2 domain. We show that the neurodevelopmental disease-associated M548T mutation, which resides in the RRM2 domain, is less soluble and impairs the cryptic splicing and RNA binding ability of MATR3. In parallel, we show that the ALS-linked S85C mutation reduces solubility but does not impair RNA binding ability. Our data demonstrates that MATR3 binds to target transcripts to repress the inclusion of target exons using its RRM2 domain, and that the two disease-associated mutations differentially affect MATR3 properties and/or splicing ability, which may lead to two different consequences. Altogether, our studies establish a role for MATR3 in cryptic splicing and provides insights into how disease-associated mutations impact MATR3 splicing function and cause disease.

P1-C-57: *Investigating how the ALS-linked S85C mutation in MATR3 causes neurodegeneration*

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease associated with muscle weakness and paralysis. One genetic cause of ALS is a mutation in the gene encoding the nuclear matrix protein MATR3. MATR3 is an RNA-binding protein implicated in mRNA splicing. The autosomal dominant S85C mutation is the most common ALS-linked mutation in MATR3. We generated MATR3 S85C knock-in mice which recapitulate key ALS features such as Purkinje cell degeneration and neuromuscular junction (NMJ) denervation, and found that reduced MATR3 staining is associated in these degenerating neurons. However, the course of early disease process and disease progression remained undetermined. I found that Purkinje cells begin to degenerate as early as 20 weeks old, while NMJ deficits present as early as 30 weeks. Intriguingly, MATR3 loss begins as early as 3 weeks in Purkinje cells and 5 weeks in the α-motor neurons. These results suggest that loss of MATR3 is the key initiating event driving neurodegeneration. Future studies include determining the gene expression changes upon MATR3 loss in affected neurons using RNA-seq. Determining how neurons are degenerated in our mouse model would be vital to understanding how MATR3 S85C causes ALS.

P1-C-58: *Compromised stress granule response in the CNS of TDP-43 M337V mice*

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Responding effectively to external stress is crucial for neurons. Defective stress granule dynamics have been hypothesized as one of the faulty pathways that renders motor neurons in amyotrophic lateral sclerosis more prone to early death. However, the vast majority of stress granule studies have been performed in vitro in non-neuronal cell lines. Here, we present an in vivo stress paradigm in mice that effectively triggers the eIF2 pathway and the formation of stress granules in the CNS. Moreover, while stress granules are robustly observed in non-transgenic mice, they are much less pronounced in 18-month-old mice and TDP-43 M337V mice. Interestingly, in the well-studied SOD1 G93A mouse model, stress granule formation proceeds normally. We suggest that one reason for the defect in stress granule formation is due to a loss of the stable interaction network between RNA binding proteins and mRNA that is required for phase separation. Overall, our results indicate that mutant TDP-43 expression is associated with a defect in stress granule assembly in vivo, which could be relevant to ALS pathogenesis.

P1-C-59: *Chronic activation of SK channels precipitates depressive like behavior and cognitive deficits accompanied by reduced klotho activity in aged mice but not in young mice.*

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Recent clinical evidence suggests that late-life depression (LLD) is an early sign, a prodrome of an emerging age-dependent cognitive dysfunction. The precise causes are unknown but likely implicate overlapping pathophysiology with cognitive impairment. Direct experimental evidence with potential prodromal biomarkers is yet to be demonstrated. We investigated the activity of an inhibitory potassium channel called SK channel (SKC). The subtype SK3 has been shown to progressively increase as a function of age and underlies LTP-related deficits, age-dependent cognitive impairment, and hippocampal shrinkage, which could be related to alpha klotho protein. This antiaging protein modulates SSRI activity. In this study, we mimicked the age-dependent overexpression of SKC by repeated activation using a potent SK agonist 1EBIO in two different age groups; young (3 months) and aged (12 months). Using a battery of behavioral tests, aged animals treated with 1EBIO showed depressive-like behavior and cognitive deficits compared to controls. This effect was accompanied by a significant reduction of klotho activity measured by ELISA in the hippocampus but not in the prefrontal cortex or dorsal raphe nucleus. Based on the results, we conclude that the chronic activation of SKC mimicking overexpressed condition robustly precipitated a comorbid cognitive

dysfunction-LLD type behavior in an age-dependent manner. Therefore, SK channels can be targeted to develop a novel therapeutic intervention for LLD-cognitive dysfunction.

P1-C-60: *A clinically relevant ERK pathway inhibitor reverses core deficits in mouse models of autism and Fragile X syndrome*

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Extracellular signal-regulated kinase (ERK/MAPK) pathway in the brain is a critical convergent node in the development of autism spectrum disorder and fragile X syndrome, the leading monogenic cause of autism. However, it is not clear whether directly and selectively targeting this pathway is beneficial in these diseases. Here we tested a clinically relevant, selective inhibitor of ERK signaling in two mouse models, one for fragile X and one for idiopathic autism. We report that this inhibitor dose and duration-dependently reversed core disease-modeling deficits in behavioral, biochemical, and electrophysiological domains in both mouse models. Further analysis revealed that sub-chronic treatment with the inhibitor in juvenile mice did not affect weight gain, locomotion, or neuronal density in the brain. Together, our data indicate that specifically inhibiting the ERK pathway is beneficial in both syndromic and idiopathic models of autism, and suggest that selectively targeting this pathway could be a new approach for both fragile X and autism.

P1-C-61: *Downregulation of Thioredoxin-1 is sufficient to induce neuronal laminopathy and molecular damage reported in neurodegenerative diseases*

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Alzheimer's Disease (AD) is the most common form of Dementia. Although, progressive neuronal loss is the major cause for the disease, the etiology of AD remains controversial. Excessive oxidative stress, formation of neurofibrillary tangles, and accumulation of Amyloid beta plaques have been traditionally targeted as the cause of neuronal loss in many experimental and clinical trials; however, there is currently no effective treatment available for AD. Trx1 is a small redox protein responsible for regulating the redox status of cellular proteins. Lowered Trx1 level has been reported in AD, although the cause remains unknown, Previous reports from our lab shown that genetic inhibition of Trx1 system impairs autophagy. We also have identified that loss of Trx1 is an important upstream event in induction of neuronal nuclear lamina invagination. Nuclear lamina damage or laminopathy is a

newly identified mechanism in pathophysiology of AD. In the current studies we use genetic inhibition of Trx1 in SH-SY5Y cells and examine the nuclear events. Our results indicate that downregulation of Trx1 is sufficient for induction of caspase 6 and NL damage. Moreover, nuclear laminopathy is associated with DNA damage, activation of cGAS-STING pathway, alteration in DNA methylating enzymes, and re-emergence of endogenous retroviruses. NL damage was partially rescued using a Thioredoxin mimetic peptide (CB3N; Ac-Cys-Pro-Cys-amide). This study provides a mechanistic link between oxidative stress and induction of cellular senescence which might contribute to the pathophysiology of AD.

P1-C-62: *Meso-limbic DA neurons as drivers of rapid cycling in bipolar disorder*

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48hr cycles in mood and sleep/arousal with profound regularity have been reported for some bipolar disorder (BD) subjects that even persist under conditions of time isolation. This indicates that the driver(s) of these oscillations must be endogenous, notably however, the one known timer in this context, the circadian clock, seems uncapable of generating such long-period rhythms. We therefore propose that 48hr cycling in BD is driven by an oscillator that is different from the circadian clock. We have previously shown in mice that disruption of the dopamine transporter leads to the emergence of a second rhythmic locomotor component (2ndC) that is distinct from circadian rhythmicity. This 2ndC can also be induced by chronic treatment with methamphetamine (Meth). Here we show that the emergence of this 2ndC requires the presence of tyrosine hydroxylase (TH) in DA neurons of the ventral tegmental area (VTA). While intact animals exhibit a 2ndC that frequently reaches 48hr periodicities in response to Meth, this capacity was completely abolished upon TH gene disruption selectively in the VTA. Considering that 48hr mood cycling is a BD-specific aberration and given that DA antagonism is an effective treatment in BD, our findings suggest that the 48hr behavioral rhythm in humans and mice are likely driven by an oscillator process that crucially relies on the ability of VTA neurons to produce dopamine. Furthermore, due to its tunability, action by this dopaminergic oscillator might be a general requirement for cycling in BD.

P1-C-63: *Tau pathology in the entorhinal-hippocampal circuit*

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The lateral entorhinal cortex (LEC) is the site of tau accumulation in early stages of Alzheimer's disease and has projections downstream to the dentate gyrus (DG) of the hippocampus. The pathological form of tau has the ability to propagate across synapses, spreading to connected brain regions and correlating with memory deficits and synaptic loss. Downstream to the LEC, the hippocampal DG is the site of ongoing adult neurogenesis, with new granule neurons added showing enhanced plasticity and increased survival compared to older neurons. We are interested in examining the role of neuron age for vulnerability to tau pathology in the LEC-DG circuit. We use an inducible cre-recombinase transgenic mouse model to label neurons born at different ages (development vs. adulthood) with TdTomato, and viral AAV Tau injections into the LEC to mimic early, localized tau pathology. Following a 4-month incubation, animals are tested for memory deficits specific to the LEC and hippocampus with Novel Object Recognition (NOR) and Novel Place Recognition (NPR) and tissue is immunohistochemically processed to analyze tau levels and cellular morphology in TdTomato-labelled DG neurons. We assess synaptic changes in DG neurons via measuring dendritic spines, dendritic complexity and mossy fibre boutons. Our findings demonstrate that tau animals perform worse on NOR compared to healthy controls, while no difference is found for NPR. Morphological results show adult-born neurons have an increase in thin dendritic spines and decrease in mushroom spines in tau animals relative to controls, as well as reduced mossy fibre bouton filopodia length. Our initial results demonstrate the effect of tau on the LEC-DG circuit, with altered synaptic structures and memory performance.

P1-C-64: *A study of human mutations in the gene encoding tyrosine kinase receptor EPHB2*

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Aberrant neural development results frequently in neurological disorders affecting nervous system function and may even be fatal. In the nervous system, contact-mediated cell to cell signaling between Erythropoietin-producing hepatoma receptor tyrosine kinases (Eph RTKs) and Eph-receptor interacting ligands (Ephrins), so-called the Ephrin-Eph signaling, regulates axon guidance and synaptic function. Dysfunction of EphB2 has been shown to generate neurodevelopmental defects in animal models. However, to date, there is no credible cohort of patients with EPHB2 mutations and nervous defects. Thus, the link between neuropathology and human EPHB2 mutations remains tenuous. A worldwide network of clinicians, assembled a cohort of patients with mutations in the EPHB2 gene, sharing corpus callosum defects. Protein sequence alignment suggests that many of our mutations are located at highly conserved sites across species and Eph receptor paralogues. Based on these human EPHB2 mutation profiles, we proceeded with functional assays on EphB2. Our data show that one mutation, located at the ligand-binding domain, decreases surface EphB2 expression and ligand binding. Structure analysis suggests that this mutation causes protein misfolding and reduces binding

affinity with B-type ephrins by abolishing disulfide bond formation. Our results suggest that mutations in the gene encoding the human EphB2 receptor could be a risk factor for corpus callosum neurodevelopmental defects in humans.

P1-C-65: *Neuronal laminopathy in hippocampus is associated with neurodegeneration and glial activation*

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Neuronal laminopathy (NLP) is newly identified in pathophysiology of Alzheimer's disease. NLP is induced by damage to nuclear lamina, a protein network at the interface of inner nuclear envelope and chromatin. NLP is detectable in most hippocampal neurons from autopsy samples in AD patients. We recently discovered that NLP is mediated by activation of caspase-6 after downregulation of Thioredoxin -1 protein (Trx1). Trx1 is a major regulator of redox balance by donating two electrons from its active site to rejuvenate oxidized proteins. Trx1 level is decreased in autopsy from AD samples. Using a Cre-recombinase system we developed a mouse model harboring a neuron specific Trx1-knockout. These animals can live up to 10 weeks and show signs of movement deficits. Here, we examined the cellular and molecular changes in hippocampus from 8-week-old mice and confirmed that induction of NLP in hippocampal neurons was associated with significant decrease in Trx1. Higher levels of Tau phosphorylation and increased total amyloid beta was also detected in these mice. Trx-1 deficient mice also contained elevated levels of phosphorylated TDP-43 (Tar DNA binding protein 43); a marker associated with neurodegeneration. Evidence of activation of astrocytes and microglia as well as oligodendrocyte damage and significantly lowered levels of myelin basic protein were detected. These animals showed lower neurogenesis capacity in the adult-derived neural stem cells from Dentate Gyrus. Our study provides a direct link between decreased antioxidative capacity with development of neurodegeneration characteristic markers.

P1-C-66: *Contribution of alpha5-GABAA receptor positive allosteric modulation on cognitive functions and neurotrophic effects.*

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Reduced GABA/somatostatin (SST) signaling is reported in psychiatric, stress-related, and neurodegenerative disorders. SST+ interneurons from cortical layers and the hippocampus inhibit the dendrites of excitatory neurons, largely through alpha5-containing GABAA receptors (a5-GABAAR). We showed that an a5-positive allosteric modulator (a5-PAM) alleviates working memory deficits and reverses neuronal atrophy in old mice. Here, we investigated the behavioral and neurotrophic effects of this a5-PAM in animal models of aging, chronic stress, and beta-amyloid load. Three studies are presented, with ~12 mice/group, 50% female: 1) Young C57BL6 subjected to chronic mild stress (CMS) to induce cognitive deficits; 2) 20 month-old C57BL6 with an exciting cognitive decline; 3) 5xFAD transgenic mice with progressive amyloid-related cognitive decline. In all studies, efficacy of chronic administration of GL-II-73 (30mg/kg, p.o, for 4 weeks) at rescuing cognitive deficits across 3 domains was assessed. Working memory was assessed in an alternation task, spatial memory in the water maze, and cognitive flexibility in a set-shifting assay. Brains were then stained using Golgi-Cox technique (n=4brain/group; 8cell/brain) for quantification of dendritic length and spine density in the prefrontal cortex and hippocampus (NeuroLucida). Chronic treatment reversed cognitive deficits across domains in each model (ps<0.01) and reversed dendritic/spine shrinkage at apical and basal dendrites (p<0.001 in PFC and CA1) in all models. Together, results support selective α5 targeting of GABAA receptors to overcome chronic stress-, aging- or amyloid-related cognitive deficits and detriments in neuronal morphology, suggesting symptomatic and disease-modifying therapeutic potential for a5-PAMs.

P1-C-67: *Therapeutic Role for Nrf2 in a Stress-Induced Rat Model System of Depression*

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Current treatments for Major Depressive disorder (MDD) primarily rely on the regulation of individual neurotransmitters and often demonstrate poor clinical efficacy. Dimethyl fumarate (DMF), an activator of the Nrf2 anti-inflammatory pathway and therapeutic for multiple sclerosis (MS), has shown potential in reducing inflammatory insult, improving cognition, and reducing depression-like behaviour in various degenerative rodent models. In this study, using the chronic unpredictable mild stress (CUMS) rat model of MDD, the sex-specific antidepressant effects of DMF were evaluated and the impact on stress-induced learning and memory deficits characterized. MF (25mg/Kg) was administered orally in 1g of peanut butter daily throughout CUMS. Results from male rats showed that, compared to CUMS controls, DMF enhanced sucrose preference (P=0.02) and increased active escape behaviour in the forced swim test (P=0.0008). DMF did not improve anxiety measures taken in the elevated plus maze or novelty-suppressed feeding test. Examining learning and memory, DMF improved spatial and recognition memory in the object location (P=0.003) and novel object recognition tests (P=0.019) respectively. These results demonstrate that DMF has antidepressant

effects and, further, alleviates stress-induced learning and memory deficits, providing merit for the repurposing of DMF for MDD. Ongoing studies will characterize responses in females, obtain measures for non-stressed controls, and determine any sex-specific and brain regional effects on cellular architecture and inflammatory cytokine expression.

P1-C-68: *Transcriptional dissection of symptomatic profiles across the brain of men and women with MDD*

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OBJECTIVE - Major Depressive Disorder (MDD) is a leading cause of disability worldwide with poorly effective therapeutic strategies. The expression of specific phenotypes could be associated with the activity of distinct transcriptional signatures in the brain. However, whether these signatures could be associated with the expression of specific symptomatic profiles of MDD is still unknown. In this study, we aimed to test whether transcriptional profiles are associated with the expression of symptomatic features in men and women with MDD. METHODS - We used the RNA extracted from 86 post-mortem brain samples across six brain regions in men and women with and without MDD along with patients' symptomatic descriptions. We used weighted gene co-expression network analysis to create region- and sex-specific gene networks related to MDD. Finally, we paired transcriptional profiles with symptomatic information to discover their associations. RESULTS - Our analysis identified gene networks enriched for differentially expressed genes (DEGs) in men and women with MDD across six brain regions. In spite of small overlaps in DEGs between men and women with MDD, further analyses suggest this may be specific to the limbic and less to the cortical regions. Pairing networks with symptomatic profiles revealed several associations between region- and sex-specific networks and symptoms. CONCLUSION - Our findings suggest that the expression of specific symptoms of MDD can be associated with the activity of sex-specific gene networks in distinct brain regions. This provides novel information on the molecular mechanisms underlying the functional changes observed in the brain of men and women expressing distinct clinical manifestations of MDD.

P1-C-69: *Temporal dissection of Rai1 function reveals brain-derived neurotrophic factor as a potential therapeutic target for Smith Magenis syndrome*

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Haploinsufficiency of retinoic acid-induced 1 (RAI1) is responsible for Smith-Magenis syndrome (SMS), a childhood neurodevelopmental disorder associated with hyperphagia, obesity and autistic features. Constitutive inactivation of one or both copies of Rai1 in the germline or developing brain induces SMS-like neurobehavioral deficits and obesity in mice. By contrast, the postnatal function of Rai1 is unclear. Here, we globally deleted one or both copies of Rai1 during two postnatal developmental windows by generating an inducible Rai1 knockout mouse model. We found that delayed Rai1 deletion at 3 or 8 weeks of age had no effect on neurobehavioral functions but resulted in adult-onset obesity and decreased expression of brain-derived neurotrophic factor (Bdnf) in the hypothalamus. Remarkably, genetic overexpression of human Bdnf in Rai1 heterozygous mice reversed SMS-like obesity, hyperphagia, metabolic syndrome-like features and hyposociability. Increasing Bdnf signaling in the paraventricular nucleus of the hypothalamus or the ventromedial nucleus of the hypothalamus was sufficient to mediate the anti-obesity effect. Our work identifies the function of Rai1 in different temporal windows after birth and provides in vivo evidence that increasing Bdnf signaling is therapeutically effective in a preclinical mouse model of SMS.

P1-C-70: *ALS dermal fibroblast derived exosomes increase wound healing*

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Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease leading to paralysis and death 2 to 5 years after symptoms onset. At present, ALS is diagnosed after clinical observation of irreversible motor deficits. Therefore, developing therapies becomes difficult as the disease is already well established upon diagnosis. When Charcot first described ALS, he made observations on patient's skin noticing that they didn't develop bedsores as most bedridden patient's do. Other observations have been made since, linking skin abnormalities in patients. It has been shown by our team that exosomes, isolated from 3D fibroblast-conditioned culture media, contained many proteins and factors associated to extracellular matrix (ECM) assembly and remodeling. With these observations, we hypothesized that ALS dermal fibroblast-derived exosomal cargo could also increase wound healing. Exosomes were characterized and scratch test assays were performed using dermal fibroblasts isolated from ALS patients and controls. Exosomal content was assessed by mass spectrometry (MS) and bioinformatics. A significant increase in cell migration was observed when adding patient-derived exosomes on monolayered scratched cells. MS and software analyses revealed that ALS exosomal proteins were more associated ECM formation and cellular migration. These findings revealed a novel exosome-dependant ECM deposition mechanism and suggest using 3D-fibroblast cellular culture may prove as an innovative approach in precision medicine to study the role of exosome and patient derived ECM proteins in ALS. Our data suggests that dermal fibroblast-derived

exosomes may participate in wound healing processes and could explain Charcot's observation on the development of bedsores in ALS patients.

P1-C-71: *Behavioral and Neurostructural Changes Associated with Chronic Amygdala Hyperactivation*

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The amygdala (AMY) is a critical limbic region showing hyperactivation in anxiety and depressive disorder patients. While acute AMY activation results in anxiety deficits, the effects of chronic hyperactivation of amygdala (cHOA) are unknown. Here we determined if cHOA is sufficient to induce depressive-like deficits or is a susceptibility factor for chronic stress-induced behavioral, volumetric and synaptic deficits. To answer this question, we used chemogenetics to chronically activate basolateral amygdala (BLA) glutamatergic neurons, subjected mice to chronic restraint stress (CRS) and assessed anxiety- and anhedonia-like behaviors weekly. Brains were ex vivo-magnetic resonance imaging (MRI)-scanned and analyzed for synaptic puncta density changes. cHOA mice displayed a progressive increase in anxiety-like deficits but no weekly anhedonia changes. CRS exposure did not exacerbate cHOA effects in any tests. MRI revealed no significant structural changes between groups. We also found that mice with prior cHOA exposed to CRS displayed an increase in synaptic puncta density in the BLA. Neuronal activity (indexed by FosB cells) positively correlated with behavioral emotionality and increased after CRS or cHOA alone but was not exacerbated in combined conditions. Our findings suggest cHOA and resulting chronic elevated anxiety did not lead to depressive-like behavior or was not a susceptibility factor to the behavioral and cellular effects of stress. This work supports AMY hyperactivity as a biomarker for anxiety disorders but bring into question its validity for depression.

P1-C-72: *A sex-specific role for prefrontal cortical EphA2 receptors in the regulation of anxiety and depression-like behaviour and neuronal oscillatory function in rats*

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Ephrin receptors are expressed in various brain regions implicated in depression and are involved in the regulation of synaptic transmission, dendritic spine morphology, and inflammatory responses. In this study, the role of the EphA2 receptor (EphA2R) in the sex-dependent regulation of anxiety and

depression-like behaviour, and on neurophysiological systems function, in rats was evaluated. Rats were administered an intra-prefrontal cortex (PFC) infusion of an EphA2R peptide agonist (0, 5 nmoles/side) prior to behavioural testing in the forced swim test, sucrose preference test, or elevated plus maze. Local field potentials were taken from the dorsal hippocampus, cingulate cortex, and nucleus accumbens, and PFC tissue taken for analysis of EphA2R signalling. PFC EphA2R activation induced depressive- and anxiety-like behaviour and increased PFC ephexin-1 activity, a downstream substrate of the EphA2R, selectively in female rats. The effects of PFC EphA2R activation on spectral power and coherence were predominantly focused within the low frequency range in both males and females but showed distinct regional specificity depending on the sex. Further, we observed increased theta band coherence involving the cingulate cortex selectively in the female rats. Overall, these findings implicate EphA2R-ephexin-1 signaling in the PFC as potentially having a unique female-specific role in regulating behaviours that may have relevance to depression, and further, highlight the critical need for the inclusion of sex as an experimental variable in research.

P1-C-73: *Xlr4b expression in corticoaccumbal and corticotegmental pathways elicits different depressive-like behaviors in males but not in females.*

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Background. The medial prefrontal cortex (mPFC) is part of a complex circuit controlling stress responses through its projections to limbic structures including the nucleus accumbens (NAc) and ventral tegmental area (VTA). We recently showed through RNAseq that chronic stress induces Xlr4b gene expression in the corticoaccumbal and corticotegmental pathways of males but not females. In this study, we aimed to characterize the behavioral effects of Xlr4b overexpression in these two pathways in both sexes. Methods. We used an intersectional viral approach to specifically express Xlr4b in either corticoaccumbal or corticotegmental pathways before assessing different depressive-like parameters such as anxiety, behavioral despair, and anhedonia in naive mice and after a subthreshold chronic variable stress (sCVS). Results. Xlr4b expression in the corticoaccumbal pathway induced anxiety (assessed with the novelty-suppressed feeding test and the elevated plus-maze test) and behavioral despair (in the splash test and the forced swim test) in subchronically stressed males but not females. Its expression in the corticotegmental pathway elicited anhedonia (assessed with the sucrose preference test) after sCVS in males but not in females. Conclusion. Our results suggest that pathway-specific overexpression of Xlr4b increases stress susceptibility in a sex-specific fashion, recapitulating anxiety and behavioral despair when expressed in NAc-projecting mPFC neurons and anhedonia in VTA-projecting mPFC neurons of males but not females. Modification of this gene expression is sufficient to recapitulate the behavioral alterations observed in chronically stressed animals.

P1-C-74: *Exploring remote ischemic postconditioning as a therapeutic intervention to promote remyelination in white matter injury*

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Remote ischemic postconditioning (RIPostC) is a therapy that involves cycles of ischemia followed by immediate reperfusion in local tissue, which confers a global reparative/protective phenotype. This global protection is conferred to multiple systems, including the central nervous system (CNS). The assessment of remote conditioning as an intervention in the context of white matter repair has not yet been explored. The RIPostC model was established using two custom sphygmomanometers on C57Bl6 mouse hindlegs. Tissue proteomics and bulk RNA sequencing were used to observe changes in the spinal cord of animals that received single or repeated conditioning. Next, daily RIPostC is performed following LPC-induced demyelination in the mouse T3-T4 intervertebral space. Immunohistological staining was used to further investigate changes within the lesion microenvironment. In the naïve spinal cord, RIPC significantly changes the proteome and transcriptome. Pathway analysis shows changes in angiogenesis signalling, antioxidant pathways and remyelination. Additionally, the mouse serum profile is significantly changed with repeated conditioning. We then used the LPC-demyelination model to evaluate RIPostCs effects on the lesion. Histological staining revealed a decrease in lesion size following repeated intervention. RIPostC significantly modified the cellular response to injury within the lesion, including changes to oligodendrocyte and microglia expression. We are the first to demonstrate changes following repeated remote conditioning in the proteome and transcriptome in the mouse CNS. Additionally, RIPostC has demonstrated potential to be a therapeutic intervention for white matter protection in the LPC animal model.

P1-C-75: *Sensory-evoked activity in somatosensory cortex as a model to probe cortical plasticity in a mouse model of Rett syndrome*

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We studied a form of activity-dependent plasticity in Mecp2 mutant mice to better understand the loss of MECP2 function in neuronal circuit and sensory processing. Primary hindlimb (HL) somatosensory cortical evoked responses (CER) to vibratory stimulation were assessed by Intrinsic Optical Signaling (IOS) imaging and intracortical local field potential (LFP). CER were assessed before, during, and after 1 hour of repeated HL vibratory in symptomatic male and female and pre-

symptomatic young female RTT model mice. After 1-hour, CER to test vibrations were reduced by approximately 40% in RTT and WT mice as assessed by both methods. Recovery of the IOS responses and LFP (300μm below pia) were tested at 15-min intervals for 1-hour after ceasing the repeated stimulation. Reduced responses persisted for at least 60-min in WT but recovered to 90-100% of normal within 15-30 min in mutant. Analysis of the LFP responses within the test train indicated that the reduced CER sensitivity during and after continuous stimulation resulted primarily from an increase in short-term adaptation during the 7-stimulus test train, that was retained in WT but reversed rapidly in RTT. We propose persistent sensory adaptation mediated by increased short-term adaptation may reflect enhanced feedback by inhibitory elements of circuits within the sensory pathway. The rapid recovery of responsiveness to repeated tactile stimulation in young female mutant mice may therefore reflect a deficit in the capacity for activity dependent plasticity to consolidate. Understanding this simple form of plasticity may therefore provide a platform to understand some of the circuit level substrates of learning and cognitive deficits in RTT patients.

P1-C-76: *Investigating the role of PTEN signalling in brain development and pediatric epilepsy using human neurons and brain organoids*

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Pediatric epilepsy affects 1 in 200 children in Canada. While antiepileptic drugs remain the first-line treatment, many patients become drug-resistant, necessitating a new paradigm of modeling and drug development tailored to human epilepsy. Recent studies discovered somatic mosaic mutations along the PTEN-mTOR pathway in pediatric epilepsy patients, but how these mutations underlie epileptogenesis remains elusive. Using CRISPR/Cas9 mediated gene editing, we have engineered human pluripotent stem cells (hPSCs) to carry PTEN loss of function mutations similar to those in human patients. We differentiated these hPSCs into neurons and brain organoids to model morpho-functional development of seizure activity in vitro. Using morphological tracing and patch-clamp electrophysiology, we showed PTEN mutant neurons have a larger soma size accompanied by hyperexcitability. Recordings from multi-electrode arrays indicated PTEN mutant neurons are hyperactive and hyper-synchronized. The molecular mechanisms behind these phenotypic differences are currently under investigation to ascribe the contribution of mTOR downstream pathways. This line of work is complemented with mosaic brain organoids and the xenografted mouse model to more closely mimic patient conditions. Together, this study will utilize multiple in vitro models to better understand the roles of PTEN in brain development and epileptogenesis to advance novel therapeutics for pediatric epilepsy.

P1-C-77: *Age is more than just a number (of spines): Adolescent mice display unique behavioural, neuronal, and neuroinflammatory responses to repetitive mild traumatic brain injury*

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Mild traumatic brain injuries (mTBI) are a prevalent health issue in Canada, especially in adolescent populations. Prevailing thought suggests that the adolescent brain is more plastic, adaptable, and resilient to injury. This however may not be the case; following TBI a microglial response can remain chronically primed and activated for up to a year in humans. Additionally, microglia are key regulators of synaptic pruning during critical developmental periods. We compared 115 female and male, adolescent (P48) and adult (P180), C57Bl/6 mice in their response to repetitive mTBI (RmTBI). On post-injury days 1-3 (PID1-3) animals underwent a behavioural test battery to assess motor deficits, anxiety-like behaviour, and cognitive functioning. On PID5 immunohistochemical techniques were utilized to assess microglia activation (Ionized-binding calcium adaptor molecule 1; Iba1) and neuronal analysis of dendritic spine density. Here, we found statistically significant age- and sex-dependent behavioural symptoms (p's < .05). Additionally, there were age-, sex-, and injury-dependent changes in spine density and Iba1 expression (p's < .05). These divergent results in adults and adolescents suggest that adolescents are not small adults; they exhibit unique responses to RmTBI. Altering microglial phenotypes and subsequent synaptic density may have life-long consequences and lead to the early onset of cognitive disorders such as dementia. Therefore, characterizing age-dependent behavioural, neuronal, and neuroinflammatory responses will be key to developing effective therapeutics.

P1-C-78: *Regional differences in cerebral white matter phospholipid fatty acid composition: a study of child abuse and age*

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Introduction: Child abuse (CA) is the primary preventable risk factor for the development of mental illness. Severe CA has been specifically linked with long lasting disruptions of oligodendrocyte and myelin function. The myelin sheath is highly enriched in lipids and CA-related myelin findings may represent alterations of its lipid profile, especially given that the composition of fatty acids (FA) in myelin phospholipids influence its compactness, stability, and permeability. Notably, there is a paucity of information on FA composition in cortical white matter (WM) compared to long-range fiber bundles. Therefore, the objective of this study is to quantify FA concentrations in the postmortem human

anterior cingulate cortex (ACC) WM as well as the uncinate fasciculus (UF), a major association fiber tract. Methods: In both regions, the FA concentrations in the choline glycerophospholipid (ChoGpl) pool were compared between depressed suicides with a history of CA, depressed suicides without CA, and non-psychiatric controls. Group-matched brain samples were provided by the Douglas-Bell Canada Brain Bank. Total lipids were extracted according to the Folch method, lipids were separated into respective classes using thin-layer chromatography, and FA methyl esters from each fraction were quantified using gas chromatography. Results: Our analysis of the ACC and UF ChoGpl fractions revealed divergent patterns of FA composition with respect to both CA and age. These results, as well as those concerning the FA composition of other UF phospholipid fractions, will be presented. Conclusion: These findings are the first to characterize regional heterogeneity in WM FA composition and to associate CA with ChoGpl dysregulation in the human brain.

P1-C-79: *A subset of aged mice develops cognitive decline associated with prefrontal cortex synaptic alterations*

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Aging is the most impactful risk factor of neurodegeneration and has been associated with a decline in several cognitive functions. These include working memory, decision making, planning and executive functions controlled by the prefrontal cortex. Previous studies revealed that age-dependent memory impairments are correlated to an imbalance in prefrontal synaptic activity towards inhibition. However, it remains elusive whether these changes in the inhibitory tone are associated with pre- or postsynaptic changes and whether by manipulating the synaptic activity, we can alleviate any age-dependent cognitive impairments. Thus, we characterized old and young mice behaviorally and measured the levels of several excitatory and inhibitory synaptic proteins. Approximately 50% of the old mice showed impaired novelty-based non-spatial memory. These old bad performers (BP) also exhibit anxiety-like behavior in the open field arena test and social impairments in an unconditioned social behavior test as compared to the old good performers (GP) or the young mice. Moreover, the ratio of PSD95 to Gephyrin protein levels was significantly lower in the BP whereas the levels of VGAT were significantly higher in the BP as compared to young mice. Optogenetic activation of the prefrontal cortex in old Thy1::ChR2-EYFP mice augmented non-spatial memory but suppressed explorative behavior. Finally, activation of cortical inhibitory neurons in young Gad2::ChR2-EYFP mice was detrimental for novelty based memory but had no effect in old mice. Finally, optogenetic stimulation of old Gad2::ChR2-EYFP mice resulted in social interaction deficits.

P1-C-80: *The synaptic organizer cerebellin 1 impedes amyloid-β oligomers deposition in the cerebellar granule cells*

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Amyloid-β (Aβ) is a key molecule involved in the pathogenesis of Alzheimer's disease (AD), the most common neurodegenerative disease. Earlier researches have shown that the cerebellum is relatively spared from amyloid deposition compared to other brain regions. Furthermore, cerebellar neurons are resistant to the neurotoxic effects of Aβ oligomers (AβOs). We have previously identified that AβOs bind to presynaptic adhesion molecules neurexins (NRXs). NRXs orchestrate synapses development in the cerebellum through formation of trans-synaptic molecular bridges with secreted cerebellin 1 (Cbln1) and postsynaptic GluD2. Interestingly, AβOs and Cbln1 share the same binding domain on NRXs suggesting a competitive binding dynamic. Thus, we hypothesize that endogenous Cbln1 is preventing AβO accumulation in the cerebellum by blocking the interaction between AβOs and NRX. Indeed, our cell surface binding assays revealed that application of Cbln1 completely abolished the binding of AβOs to NRX, but AβO application did not disrupt NRX-Cbln1 binding, suggesting that NRX-Cbln1 complex is resistant to AβOs. Furthermore, AβO treatment in Cbln1 knockout cerebellar neurons showed a significant increase of AβOs deposition on axons compared to wild-type neurons, and this increase was cancelled by exogenously-applied Cbln1 recombinant proteins, suggesting that endogenous Cbln1 could protect cerebellar neurons from AβOs. This study may uncover a new mechanism that promotes selective cerebellar resistance to Aβ-induced pathological mechanism in AD.

P1-C-81: *Efficacy of prophylactic versus therapeutic administration of the NMDA receptor antagonist MK-801 on the acute neurochemical response to a concussion in a rat model combining force and rotation*

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The aim of this study was to investigate the efficacy of prophylactic versus therapeutic administration of MK-801, a promising NMDA receptor antagonist, on the acute changes in amino acid extracellular concentrations involved in excitotoxicity resulting from a concussive trauma. Our previously validated combination of a weight-drop concussion rat model and in vivo cerebral microdialysis was used. The primary outcome included amino acid concentrations and the secondary outcome included righting time. Samples were taken in 10-min increments for 60 min before, during, and 60 min after impact,

and analyzed for glutamate, gamma-aminobutyric acid, taurine, glycine, glutamine, and serine using high-performance liquid chromatography. Righting time was acquired as a neurological restoration indicator. Physiological saline or 10 mg/kg MK-801 was administrated intraperitoneally 60 min before or immediately following induction of sham injury or concussion. Following concussion, glutamate, taurine, and glycine levels as well as righting times in cases from the MK-801 treatment group were comparable to vehicle-treated animals. In contrast, righting times and amino acid concentrations observed within the first 10 min after induction of concussion in cases assigned to the MK-801 prophylaxis group were comparable to sham-injured animals. These results suggest that presynaptic actions and peak availability of MK-801 following prophylactic administration significantly inhibit the immediate and indiscriminate release of glutamate, taurine, and glycine in extracellular fluid after a concussion.

P1-C-82: *The therapeutic potential of cannabidiol on neuroinflammation, pain sensitivity and behavioral recovery in a mouse model of multiple traumatic injuries*

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Recent studies documented the anti-inflammatory properties of cannabidiol (CBD), the main non-psychoactive cannabinoid extract, making it a promising neuroprotective agent in a variety of neurological conditions such as mild traumatic brain injuries (mTBI). The main objective of this study is to evaluate the effects of a 7-day CBD treatment on neuroinflammation, pain sensitivity and behavioral recovery after multi-trauma. Validated mouse models of trauma will be used to combine closed tibial fracture with concomitant closed head mTBI. Male mice (n = 44) will be divided into 4 groups according to 2 independent variables: Injury (mTBI+fracture vs. sham) X Treatment (CBD vs. vehicle). Neuroinflammation will be evaluated by measuring myo-inositol relative concentrations 24h following treatment and longitudinally at D35 following multi-trauma using in vivo 1H-MRS. Pain sensitivity will be assessed with the Mouse Grimace Scale, thermal (Hargreaves) and mechanical (von Frey) nociceptive withdrawal threshold tests before and following treatment (D7). Orthopedic and cognitive functions will be assessed with open field, Y-maze and rotarod tests for 3 consecutive days from D30. We hypothesize that relative to placebo, CBD treatment will significantly reduce: baseline-adjusted pain on D7, neuroinflammation on D8 and 35; functional impairment on D30. This project could provide objective animal evidence on the clinical utility of CBD interventions in treating neuroinflammatory conditions.

P1-C-83: *Functional impact of chronic stress on corticotegmental synaptic signalling*

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Cortically driven dysregulation of subcortical circuits can trigger depressive-like behaviours in humans and animals. Amongst these circuits, the medial prefrontal cortex (mPFC) sends dense projections to the ventral tegmental area (VTA). Recent findings from our lab showed that chronic stress induces functional and morphological changes to the corticotegmental pathway in a sex-dependent fashion. However, whether these sex-specific modifications result in durable alterations in the VTA of males and females remains unclear. Chronic variable stress (CVS) was used to produce a persistent depressive-like phenotype in males and females. A trans-sectional viral strategy was used to label downstream neurons in the VTA and to express excitatory opsins in corticotegmental terminals. Optogenetic stimulation on live brain slices was used to activate the cortical projections in the VTA of naive and stressed mice. Whole-cell patch-clamp experiments were performed to measure optogenetically-evoked responses in VTA neurons. Our viral approach successfully allowed us to optogenetically stimulate cortical projections to the VTA. Our analysis revealed that chronic stress interferes with the potentiation of mPFC-VTA connections normally observed after repetitive stimulation in control mice. Our results suggest that CVS interferes with intrinsic plasticity mechanisms at mPFC-VTA synapses in males and females, without affecting unitary evoked responses. Understanding these effects will provide novel insights into the neuronal mechanisms underlying behavioral adaptations to chronic stress.

P1-C-84: *Preventive strategies alleviate stress-induced depressive-like behaviors and improve intestinal barrier integrity*

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Chronic stress is a contributor to major depressive disorder (MDD). Throughout life, one in five individuals will be affected by MDD and only 30-50% of depressed patients completely remit, suggesting that neuron-based therapies do not address important biological causal factors. Chronic social stress exposure induces blood-brain barrier leakiness and establishment of depressive-like behaviors in mice. As the role of the gut-brain axis in depression is increasingly recognized, we investigated the effect of chronic stress on gut barrier integrity, if preventive strategies can promote stress resilience and the underlying biological adaptations. First, we took advantage of the classic chronic social defeat stress model and social interaction test to characterize two subpopulations of

mice: stress-susceptible and resilient. Next, beneficial effect of access to an enriched environment or physical exercise on social interactions was evaluated. Then, changes in the gut barrier integrity were measured at the transcriptional and morphological level. Our results suggest that stress resilience correlates with molecular adaptations in intestinal tight junction protein expression whereas stress susceptibility is associated with changes that could exacerbate inflammatory response leading to maladaptive behaviors. By highlighting that preventive strategies can induce positive gut barrier adaptations along with resilience despite stress exposure may open new alternatives in the treatment of depression.

P1-C-85: *DMSO and changes in hippocampal neuronal activity*

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Dimethyl sulfoxide (DMSO) is widely used in preclinical and clinical research, as it enhances the entrance of water-insoluble drug candidates into the central nervous system. DMSO suppresses the inward and outward currents by interacting with GABA receptor-Cl- channel complex. It was shown that, particularly low DMSO concentrations appear to profoundly influence neural network activities. Modulation of cell signaling by low concentrations of DMSO could also explain the differential regulation of neuronal activation in various brain regions. There is no evidence for accumulation of DMSO in the brain tissue and the elimination occurs within 12-36 h in experimental animals. Background and evoked spike activity were recorded in single neurons of the hippocampus treated with DMSO (1 ml/kg /kg, i.p., once) (n=5) in the dynamics (from 1 to 105 minutes) after DMSO exposure (after 5 minutes). The main effects lasted up to 40 and 90 minutes. In response to HFS (High frequency stimulation) of the Entorhinal cortex, the analysis revealed inhibitory effects.

P1-C-86: *Neurofibromin haploinsufficient cultured fibroblasts actively participate in the tumoral microenvironment establishment in neurofibromatosis type 1 tissue-engineered 3D skin model*

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Introduction: Neurofibromatosis type 1 (NF1) is a common monogenetic disorder caused by germline mutations in the neurofibromin-encoding gene NF1. Patients develop multiple benign skin tumors, called cutaneous neurofibromas (cNFs), which are composed of Schwann cells (SC), fibroblasts, mast cells and endothelial cells embedded by a dense extracellular matrix (ECM). Their morphogenesis is

poorly understood, and their formation can highly vary between patients. Complete loss of NF1 function alone cannot explain tumor development and several experimental studies suggest that other factors such as NF1 haploinsufficient (NF1+/-), cellular type or the stromal microenvironment may also be involved. Methods: Skin tumor microenvironment (TME) was studied using 3D cell culture and tissue-engineered skin (TES) models derived from NF1 patients. Tumor-like spheroids composed of NF1-/- SC and NF1+/- or NF1+/+ skin fibroblasts were also incorporated in our model. Exosomal protein contents, secreted by dermal fibroblasts was characterized. Various parameters, such as cell migration, angiogenesis and ECM production, were assessed. Results: NF1-derived TES were significantly thicker and more concentrated in fibronectin. NF1-/- SC exhibited spontaneous migration when inosculated in TES containing NF1+/- fibroblasts. Levels of VEGF and others angiogenic factors were highly elevated in exosomes derived from NF1+/- skin fibroblasts. Vascularization was also enhanced in NF1-derived TES. Conclusion: NF1+/- skin fibroblasts could actively participate to TME modification of cNFs by secreting more ECM and by promoting angiogenesis via exosomes.

P1-C-87: *LM11-A31 a small molecule modulator of low affinity neurothropin receptor (p75ntr) ameliorates experimental stroke injury*

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Neurotrophins have an established role in survival and differentiation of damaged neurons. Nevertheless some like the precursor molecule of neural growth factor (pro-NGF) may drive apoptotic cascades in neurons trough P75 neurotrophin receptor (P75ntr). Recent evidences indicate P75ntr modulation provides protection against neural damage, yet little is known on its implication in stroke injury. Adult mice underwent distal middle cerebral artery occlusion (dMCAO) and analyzed for P75ntr expression in penumbral region. Accordingly P75ntr was significantly upregulated in few hours and did not return to baseline by 7 days post injury (dpi). Stroke animals receiving LM11-A31 (25 mg/kg; i.p.; twice daily), a small molecule P75ntr modulator; showed remarkably lower infarct volume by dpi 3. This paralleled with improved function at handedness and adhesive removal tests. In complementary in vitro experiments, rats' primary cortical neural cells were exposed to oxygen glucose deprivation (OGD); followed by co-culturing with OGD-activated primary astrocytes; as main source of pro-NGF. LM11-A31 addition following OGD, could reduce neural damage in sandwich neuro-astrocyte cultures (20-100 nM) along with reduced NJK apoptotic signaling . These preliminary findings provides in vitro and in vivo supporting evidences for P75ntr modulation by LM11-A31 as a potential approach to ameliorate ischemic stroke damage. Keywords: P75 neurotrophin receptor, ischemic stroke, LM11-A31

P1-C-88: *2-Bromo-LSD: A non-hallucinogenic LSD analogue with therapeutic potential for Major Depressive Disorder.*

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Major depressive disorder (MDD) is the leading cause of disability worldwide. Current pharmacotherapy treatments, such as SSRI's and SNRI's, have long effective latencies, require chronic administration, and show an estimated 30% treatment resistance rate, necessitating the search for more effective, alternate treatments. Interest in psychedelic hallucinogens (e.g., lysergic acid diethylamide [LSD], psilocybin) has seen a resurgence due to their potential for the treatment of neuropsychiatric diseases, including anxiety and depressive disorders. However, psychedelics induce hallucinations which can last for hours, making efficient and cost-effective treatment difficult. Therefore, discovering non-hallucinogenic derivatives with antidepressant properties is of paramount importance. 2-Bromo-LSD (2BLSD, BETR-001) is an LSD derivative with 5-HT2A agonist activity that lacks hallucinogenic effects and has been safely used for cluster headache treatment. Here we examine the anti-depressant and neural plasticity-promoting activity of 2BLSD. Our findings demonstrate that 2BLSD reverses the depression-like behaviors following chronic variable stress in mice and promotes dendritic arbor complexity in cultured primary rat cortical neurons. These results show that 2BLSD may possess a therapeutic potential and represents a promising alternative to psychedelics in the treatment for MDD.

P1-C-89: *Dysregulated mRNA translation and schizophrenia-relevant behaviours in mice*

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Schizophrenia (SCZ) is one of the leading causes of disability worldwide. SCZ arises by alterations in neurodevelopment, involving multiple etiological factors that influence the function of several neurotransmitter systems. For example, dysfunction of the dopaminergic (DAergic) system has been consistently implicated in the pathology of SCZ. Although the role of DA has been well established in SCZ, the developmental factors that lead to dysfunctional DAergic neurotransmission are still a matter of active research. mRNA translation is a key regulator of neural development and is regulated through the mammalian target of rapamycin complex 1 (mTORC1) pathway, among others. Upon its activation, mTORC1 phosphorylates the eukaryotic initiation factor 4E (eIF4E) binding proteins (4E-BPs), allowing eIF4E to recruit the remainder of the translation initiation factors. Considering the

importance of the mTORC1-4E-BP pathway in development, we examined the role of 4E-BP2 in the mesolimbic dopaminergic system using a 4E-BP2 mutant mouse model. In male and female mice, we found that absence or haploinsufficiency of 4E-BP2 impaired pre-pulse inhibition of acoustic startle and exaggerated amphetamine-induced locomotion, compared to wildtype littermates (but no difference in locomotion induced by the NMDA receptor antagonist MK-801). These results demonstrate that 4E-BP2 plays an essential role in the development of the dopamine system and potentially in the pathophysiology of SCZ.

P1-C-90: *Examining the influence of child abuse on the microglial modulation of perineuronal nets in the prefrontal cortex of depressed suicides*

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Background: Child abuse (CA) is one of the strongest predictors of depression and suicide. Early life is characterized by critical periods (CP) of plasticity during which brain circuitry is more easily altered by the external environment. During childhood, perineuronal nets (PNNs) develop around certain neurons in the brain and concretize neuronal circuitry, closing the CP. We recently reported that a history of CA is associated with an increase in PNNs around parvalbumin interneurons in the ventromedial prefrontal cortex (vmPFC) of depressed suicides. Given that microglia have been implicated in the regulation and maintenance of PNNs, we hypothesize that CA lastingly affects microglia-PNN interactions in this cortical area. Methods: Well-characterized vmPFC samples from adult depressed suicides with or without a history of CA and matched controls were provided by the Douglas-Bell Canada Brain Bank. Matrix metalloproteinase (MMP) antibody arrays, immunoblotting for the neoepitopes of MMP cleaved aggrecan, as well as immunofluorescent (IF) labelings (NeuN, WFL, CSPG1, TMEM119) and fluorescent in situ hybridization (CD68) are being used to investigate the relationship between microglia and PNNs. Results: We found a significant downregulation of MMP-1,2,3,8,9,13 and endogenous inhibitors TIMP-1,2,4 in the vmPFC. Optimized IF staining reveal a close proximity between microglia and PNNs. Conclusions: Preliminary results suggest that microglia may play an indirect role in the maintenance of increased PNNs through dysregulation of secreted MMPs and their inhibitors.

P1-C-91: *Astrocytic signatures from whole-cell genomics data to map Alzheimer's disease progression*

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Alzheimer's disease (AD) is a leading cause of age-related dementia. Since current drug therapies cannot directly prevent the progression of AD, more hope has been placed on the early prediction of the disease. Besides the hypothesis that deposition of amyloid-beta (Aβ) and neurofibrillary tangles (NFT) is considered a hallmark of AD progression, localized hyperexcitability is observed preclinically as a precursor of Aβ deposition and in correlation with NFT development. We explore AD-related hyperexcitability emergence, characterizing the surface and cell-wide expression of astrocytic glutamate transporters (GLT1) in murine cultures for different applications (in duration and concentration) of extracellular Aβ, mimicking different AD stages. We observe that GLT1 expression in different cellular compartments changes with varying AD phases. To gain insight into the molecular underpinnings for transporter-related AD hyperexcitability, we resort to signal-enriched genomics analysis to identify differentially-expressed pathways linked with GLT1 trafficking. Through deconvolution, we infer single-cell RNAs profiles from multiple AD databases and exploit diffusion mapping to monitor the time-evolution of astrocytic gene signatures for the disease's progression.

P1-C-92: *Long-lasting impact of brief dietary lipid supplement on normalizing morpho-functional synaptic and behavioural deficits in the fragile X cerebellum*

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Fragile X Syndrome (FXS), the most prevalent monogenic form of autism spectrum disorder characterized with hyperactivity, stereotypies, and learning disabilities. There are limited clinical interventions available to treat this genetic disorder. Using mouse model for FXS, we have previously discovered an excitation and inhibition (E/I) imbalance in the cerebellum where excessive GABA release from inhibitory interneuron terminals due to the hypoexpression of Kv1.2 at the plasma membrane suppresses the output of Purkinje neurons (PN). Docosahexaenoic acid (DHA), a crucial Ω-3 polyunsaturated fatty acids, functions as a positive allosteric modulator for Kv1.2. To test the therapeutic impact of DHA, we placed juvenile wild-type and Fmr1 KO mice under DHA enriched diet for 2 weeks and assayed for changes in physiology and behaviour when they reached adulthood. We found that DHA supplemented diets produced long-lasting effects by rectifying the E/I imbalance, the behavioural anxiety, and repetitive stereotypic behaviours. Unexpectedly, not only the protein expression levels of Kv1.2, but also the morphology of the inhibitory interneuron terminals was normalized in the DHA treated Fmr1 KO mice, complemented by changes in other molecular markers

that converge to contribute to reducing the inhibitory overtone. Together, our study suggests that dietary supplementation of DHA, even brief, can rectify excessive inhibition and produce long-lasting benefits and presents a new strategy to mitigate anxiety related symptomologies in FXS and other neurological disorders.

P1-C-93: *Cell-type and sex-specific transcriptomic changes in the post-mortem dorsolateral prefrontal cortex in major depressive disorder*

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Major depressive disorder (MDD), a leading cause of disability globally, affects 200-300 million people worldwide and strongly increases the risk for suicide. Depression is more common among women, while suicide is more common among men. Patterns of depression-associated transcriptomic changes across brain regions are sex-specific in both human post-mortem studies and in animal models of depression. Further, mechanisms involving many of the highly functionally diverse cell-types in the human cortex have been linked to depression, such as imbalance in inhibitory and excitatory neuronal signaling, astrocytic dysfunction, white matter alterations, neuroinflammation, and altered blood brain barrier function. Previously, using single-nucleus RNA-sequencing (snRNA-seq) we profiled cell-type specific gene expression in 34 male subjects with or without MDD and identified a subtype of deep layer excitatory neurons and immature oligodendrocyte precursor cells demonstrating prominent differential gene expression. Here we have expanded our cohort to include 38 female subjects with or without MDD, profiling around 190,000 cells across 41 cell-type clusters. Using state-of-the art bioinformatics we have detected cell-type specific changes in gene expression within these clusters in males and females with MDD and identified the clusters with concordant and discordant depression-associated transcriptomic changes between the sexes. These results will further our understanding of cell-type and sex-specific transcriptomic changes in MDD and reveal targets for future functional studies.

P1-C-94: *AlphaB-crystallin plays a role in terminating the pro-inflammatory macrophage response in the injured aged peripheral nerve*

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Age-related declines in Schwann cell (SC) and resident and infiltrating macrophage (MΦ) function is postulated to be responsible for the poor regrowth of damaged, aged peripheral nervous system (PNS) neurons since these cells normally create a supportive environment by secreting growth and survival permissive factors (e.g., neurotrophins, cell adhesion molecules) and phagocytosing myelin and neuronal debris. We are interested in identifying the molecular factor(s) responsible for the reduced actions of SCs and MΦs in the injured, aged PNS. We found that a small heat shock protein called alphaB-crystallin (αBC) that is expressed by SCs and axons declines with age in the PNS, and this correlated with defective myelination, reduced lipid synthesis and enhanced presence of MΦs in the injured and uninjured PNS. As such, we assessed herein if the number and phenotype of SCs and MΦs were impacted by αBC in the damaged aged PNS by quantifying the number of myelinating and non-myelinating SCs, and pro- and anti-inflammatory MΦs after sciatic nerve crush injury in WT and αBC globally null mice across age. We found that not only was the total number of MΦs elevated in older αBC knockout mice at later post-injury timepoints compared to WT and younger mice, but that the enhanced number of MΦs were of a pro-inflammatory phenotype. Therefore, the natural decline in αBC with age may result in an increased presence of pro-inflammatory MΦs that could contribute to adverse symptoms such as neuropathic pain after peripheral nerve injury.

P1-C-95: *Functional and molecular architecture of the healthy and diseased human brain*

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Epilepsy is a life-altering disease, affecting up to 1 million people worldwide. Although several new anti-epileptic drugs have been introduced in clinical routine in the last decades, 30% of epilepsy patients remain pharmacoresistant. Differences between fundamental properties of mouse and human neurons, as well as failures to translate therapeutic approaches from rodent models to clinical trials, highlight the need to study physiological and pathological mechanisms directly in human brain tissue. We investigated the functional and molecular properties of neuronal subpopulations in healthy and diseased human brain specimen. Using electrophysiology, Ca activity imaging and transcriptional methods (spatial transcriptomics, single nucleus RNA-seq, multiplexed FISH), we investigated the involvement of specific subpopulations of neurons in epileptic activity ex vivo. We further investigated the functional involvement of neuronal subtypes by targeted optogenetic manipulation using viral systems in human brain slice cultures. Our results provide unprecedented insight into the spatial heterogeneity of neuronal subtypes in the healthy human brain and provide detailed information on epilepsy-associated molecular transformations in the human brain. Importantly, identifying how cell types and molecular profiles are affected by epilepsy will guide development of novel therapeutic approaches for pharmacoresistant patients suffering from epilepsy.

P1-C-96: *Sex-specific accumulation and cognitive effect of the histone variant H2A.Z in Alzheimer's disease*

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The dysregulation of gene expression has a role in cognitive deficits and neuropathology in Alzheimer's disease (AD), thus prompting interest in epigenetic factors as mechanisms of neurodegeneration and memory loss. Here, we assess the therapeutic potential of the histone variant H2A.Z, a memory suppressor that is actively removed from DNA during learning to promote gene expression and memory formation. In the aged brain, H2A.Z levels increase and may act as a prelude to age-related memory decline. We hypothesize that H2A.Z also accumulates in AD and that depletion of H2A.Z is an effective therapy for memory deficits. To characterize H2A.Z levels in the AD brain, we assessed genome wide (ChIP-seq) and site-specific (ChIP-qPCR) binding of H2A.Z to DNA as well as mRNA expression of genes encoding H2A.Z in both the human post-mortem and 5xFAD mouse hippocampus. Binding of H2A.Z increased at several memory and AD-related genes in the human patient and 5xFAD female hippocampus. This effect was sex specific, as H2A.Z binding decreased in the male AD hippocampus across species. Similarly, mRNA expression of genes encoding H2A.Z increased in the human AD and 5xFAD female hippocampus. This female-specific increase in H2A.Z was paralleled by the remediation of hippocampal-dependent spatial memory following H2A.Z depletion in 5xFAD females but not males. This first investigation of histone variants as regulators of memory in AD revealed sex-specific changes in H2A.Z that generalize across species and provides promising support for H2A.Z depletion as a therapeutic strategy in females.

P1-C-97: *TRPM3 agonists enhance neurite outgrowth in adult sensory neurons by stimulating AMPK and mitochondrial function*

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Peripheral neuropathy affects approximately 50% of the population with diabetes mellitus. It is associated with substantial morbidity and is characterized by induction of pain and loss of sensory function in limbs. Recent studies suggest that molecular cascades maintaining mitochondrial function and calcium homeostasis are effective therapeutic targets for diabetic peripheral neuropathy. Interestingly, our lab has recently reported that muscarinic acetylcholine type 1 receptor (M1R) antagonists stimulated neurite outgrowth, in part, by activating Ca2+/calmodulin-dependent protein

kinase kinase II (CaMKKII) and mobilization of AMP-activated protein kinase (AMPK). This augmented mitochondrial function in sensory neurons imparts protection against small and large fiber neuropathy in various rodent models. Transient receptor potential melastatin receptor 3 (TRPM3) is a TRP type cation channel that triggers Ca2+ influx. We hypothesized that opening of TRPM3 could activate CaMKKII and induce neurite outgrowth and may mimic antimuscarinic drug effects. Dorsal root ganglion (DRG) neurons were isolated from adult control and streptozotocin-induced type 1 diabetic male Sprague-Dawley rats. A significant dose-dependent elevation of neurite outgrowth was observed in response to pregnenolone sulphate (PS) or CIM0216 (selective and specific TRPM3 agonists, respectively) These TRPM3 agonists also increased AMPK activation and triggered an increase in the calcium influx. Mitochondrial membrane potential (ΔΨm) (using JC-1 dye) was significantly increased in response to pretreatment of PS and CIM. Our investigations of TRPM3 activation and its downstream molecular cascade will hopefully lead to potential therapeutic targets for impeding detrimental effects of peripheral neuropathy.

1D. Sensory and Motor Systems

P1-D-98: *Cortical neuroprosthesis for reversing paralysis: proof of concept in a large animal model*

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Rehabilitation after spinal cord injury facilitates locomotor recovery, but deficits often persist. In a rat model of unilateral spinal cord injury that paralyses one leg, we found that cortical microstimulation delivered during locomotor training fosters recovery of voluntary motor control. Further studies are needed to translate our findings to the clinic, including testing this strategy on clinically-relevant animal models of paraplegia. We developed a neuroprosthesis that delivers alternated microstimulation to the motor cortices during locomotion in a feline model of thoracic spinal contusion (T10) that produces long-term bilateral locomotor deficits. We hypothesize that alternated cortical stimulation will facilitate long-term recovery of voluntary locomotor control and that performance will be maintained after therapy is discontinued. After a T10 spinal contusion, once weight-supported locomotion is recovered, cats will be trained on treadmill 20 minutes per day for 3 weeks, with or without cortical microstimulation (2 groups of 8 cats). Therapy will then be discontinued for a month and cats will be tested. The long-term effect of cortical stimulation on locomotor performance and voluntary leg control capacity will be evaluated weekly on a flat treadmill, ladder treadmill and obstacle avoidance tasks, without stimulation. Our neuroprosthetic device represents a highly novel and very promising new therapeutic tool for locomotor rehabilitation. Together, this knowledge can be applied clinically to design optimal rehabilitation protocols.

P1-D-99: *Myeloarchitectonic maps of cat auditory cortex*

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The cerebral cortex contains a myriad of areas that differ in their structure and function. Delineating these areas and creating detailed maps of functional networks has been a goal of neuroscientists for over a century. While structural parcellation can be achieved using any number of features, quantifying biomarkers often depends on highly invasive histological approaches. However, novel neuroimaging sequences aim to provide non-invasive estimates of anatomical features, including myelin content. To determine whether these approaches may be useful in discriminating between cortical subregions and lamina, we quantified the myelin content of 13 areas comprising the feline auditory cortex using stereology. Infragranular, granular, and supragranular myelinated fiber length density estimates were generated for each region in 3 animals using the Spaceballs probe in Stereoinvestigator (MBF Biosciences). Our results suggest unique patterns of myelination exist across these cortical areas. Moreover, myelination gradients are in accordance with a functional hierarchy previously established using patterns of interregional connectivity. That is to say, core areas (primary auditory cortex and the anterior auditory field) show the greatest myelin density, with decreasing myelination in higher-order areas. These results suggest myelin-sensitive imaging may be useful in delineating sub-regions of cortex, allowing for more accurate brain atlasing and a more detailed understanding of the contributions that individual cortical fields make to brain function and behaviour.

P1-D-100: *Traveling UP states in the post-subiculum reveal an anatomical gradient of intrinsic properties*

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The post-subiculum (PoSub) is the primary cortical stage of the head-direction (HD) signal and one of the main inputs of the medial entorhinal cortex (MEC). The MEC is anatomically and functionally organized along its dorsoventral (DV) axis, with an increase of neuronal spatial tuning from dorsal to ventral regions as well as a gradual decrease of rectifying currents. However, whether the PoSub is anatomically organized remains poorly understood. We thus recorded populations of PoSub neurons with linear silicon probes during wake and sleep. Interestingly, we did not observe a gradient of HD tuning properties in the PoSub. However, we did observe a gradient of firing rates along this axis during non-Rapid Eye Movement (NREM) sleep, but not waking, suggesting a gradient of intrinsic

properties. NREM sleep is characterized in the cortex by periods of persistent neuronal firing ("UP" states) interleaved with periods of neuronal silence ("DOWN" states). DOWN-to-UP (DU) but not UP-to-DOWN (UD) transitions traveled from dorsal to ventral PoSub at approximately 5mm/s, and DOWN state duration increased from dorsal to ventral PoSub. To understand the mechanisms underlying this gradient, we built a computational model with a linear array of recurrently connected adapting units. The model reproduced the experimental observations with a gradient in the strength of a rectifying current, suggesting a common anatomical gradient with the MEC. These results shed light on the underlying mechanisms of UP/DOWN alternations and how spontaneous sleep activity can reveal intrinsic properties of cortical networks that are not reflected in encoded features.

P1-D-101: *Combining a cortical and spinal neuroprosthesis to restore walking deficits and improve recovery of leg control after incomplete spinal cord injury in the rat.*

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Incomplete spinal cord injuries (SCI) are associated with chronic motor deficits. Neuroprosthetic therapies can target remaining pathways to treat walking deficits. Because no study has directly compared the single and combined effect of spinal and cortical stimulation over restoration of walking, our lab recently developed a novel neuroprosthesis that stimulates the brain and spinal motor circuits in synchrony with walking. In n=6 rats, we implanted electromyographic electrodes (EMGs) within hindlimb muscles, a multi-electrode array within the hindlimb motor cortex and epidural electrodes over the lumbar (L2) and sacral (S1) spinal segments. After obtaining baselines for kinematics/EMGs on a treadmill, rats received a spinal hemisection at T9 that paralyzed one leg. We evaluated the immediate effects of cortical and/or spinal stimulation over treadmill locomotion in the intact state and after SCI. Gait analysis showed that combined cortical and spinal stimulation delivered during walking are more effective in reducing foot drop caused by SCI than cortical or spinal stimulation alone. All rats were then trained on a treadmill for 3 weeks with cortical and/or spinal stimulation. Control rats did not receive stimulation. The ladder task was used to test the recovery of voluntary control of leg movement. Rats trained with cortical stimulation, with or without spinal stimulation, displayed a higher success rate. These experiments demonstrated that cortico-spinal neuroprosthesis has the potential to reduce motor deficits and to enable targeted rehabilitation protocols after SCI.

P1-D-102: *Cell-type specific synchronization of activity in layer 5 pyramidal neurons decreases cortical information output during anesthesia-induced loss of consciousness*

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Identifying a circuit mechanism underlying the loss of consciousness induced by general anesthesia is a long-standing question in neuroscience. Activity within cortex drives conscious perception and, hence, loss of consciousness is thought to result from the disconnection of cortex. Here, we identified an aperiodic temporal synchronization of neuronal activity during general anesthesia, specific to layer 5 pyramidal neurons, a major output of cortex. This synchronous activity was maintained across different anesthetics with diverse molecular modes of action, despite having different event frequencies and amplitudes. Additionally, during transitions to and from anesthesia, the change in synchrony within layer 5 coincided with the loss and recovery of consciousness. Further, this synchronous layer 5 activity extended globally across cortex. In contrast, neurons in each of the other cortical layers, targeted through mouse Cre lines, did not show a consistent change in synchrony across anesthetics. We demonstrated that the synchronous activity in layer 5 pyramidal neurons results in a decrease in information entropy, with the entire population acting as a single effective unit. Hence, our results show that, during general anesthesia, cortex shifts from a mode characterized by spatially asynchronous outputs transmitting high information, to a mode characterized by spatially synchronous outputs, transmitting low information. This reduction in information output disconnects cortex and, thereby, provides a possible mechanism for the loss of consciousness.

P1-D-103: *Investigating the role of claustrum activity in mice locomotor behaviour*

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The claustrum is a small hyper-connected subcortical brain region. Despite intensive investigation, the precise function of the claustrum remains unclear. After the transduction of individual claustrocortical connections with a Cre-dependent GCaMP, we monitored the physiological activity of these projections in head-fixed mice running on a treadmill. In vivo fibre photometry data collected so far revealed that separate claustrum output pathways are differentially recruited by transitions between rest and locomotion. We then started to investigate the behavioural impact of claustrum modulation. We observed that genetically targeted optogenetic activation of claustrum neurons projecting to different cortical areas in mice spontaneously running on a treadmill produce significant changes in locomotor behaviour, and this effect was dependent on the claustrum projection pathway. Our data indicate that discrete claustrum neurons are recruited during movement and their activity might be necessary for efficient locomotor behaviour. With this work, we aim to provide a deeper understanding of the physiology of the claustrum and its role in the modulation of behaviour.

P1-D-104: *Exploration of the Bayesian model of tactile-spatial perception*

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The remarkable ability of the human brain to draw an accurate percept from imprecise sensory information is not well understood. Bayesian inference provides an optimal means for drawing perceptual conclusions from sensorineural activity. This approach has frequently been applied to visual and auditory studies but only rarely to studies of tactile perception. We explored whether a Bayesian observer model could replicate fundamental aspects of human tactile spatial perception. The model consisted of an encoder that simulated sensorineural response with Poisson statistics followed by a decoder that interpreted the observed firing rate. We compared the performance of our Bayesian observer on a battery of tactile tasks to human participant data. The Bayesian observer broadly replicated human performance on three spatial acuity tasks: classic two-point discrimination (C2PD), sequential two-point discrimination (S2PD), and two-point orientation discrimination (2POD). We confirmed the widely reported observation that C2PD is the least reliable method of assessing tactile acuity due to the presence of non-spatial cues. Additionally, the Bayesian observer performed similarly to humans on alphabet and braille letter-recognition tasks. The Bayesian observer further replicated two illusions: an adaptation-induced repulsion illusion and an orientation anisotropy illusion. Taken together, these results suggest that perceptual inferences may arise from a Bayesian like decoder that is unaware of the precise characteristics of its inputs.

P1-D-105: *Cortical effects of chemogenetic modulation of claustral activity using DREADDs in Thy-1-GCaMP6s mice.*

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The claustrum is an important yet understudied highly connected subcortical brain structure with connections to much of the cortex. This project examines the role of the claustrum in mediating resting-state cortical activity, connectivity, and sensory-evoked cortical responses. I performed mesoscale fluorescence imaging on anesthetized, and awake, adult mice expressing the genetically encoded calcium indicator, GCaMP6s, throughout cortex. I manipulated claustral activity using Cre-dependant Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) HM4Di/HM3Dq injected bilaterally into the claustrum and retro-Cre injected bilaterally into the prefrontal cortex to target claustral-cortical projections. Administration of clozapine-N-oxide allowed for DREADD activation and data was compared normalized baselines. Chemogenetic inhibition of claustral activity

via HM4Di increased resting-state activity in cingulate, anterior cingulate, and secondary motor cortices in both anesthetized and awake states. Inversely, claustral excitation via HM3Dq activation decreased activity in the same areas. During sensory stimulation we observed increased amplitude and area of activation in the visual cortex following visual stimulation with claustrum inhibition, an effect not seen in other sensory stimulation modalities. This data supports the hypothesis that the claustrum has a role in mediating cortical activity during both resting and sensory evoked states. This project was supported by CIHR funding to JJ (#168873) and IRW (#153111) and NSERC funding to AWC (RGPIN-2020-05988).

P1-D-106: *Sex differences in chloride homeostasis of c-fiber primary afferents in the spinal cord dorsal horn.*

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Introduction: Intracellular Cl- concentration ([Cl-]i) is high in primary sensory neurons due to the activity of the Na+-K+-Cl- cotransporter 1 (NKCC1), causing greater Cl- accumulation than typically seen in CNS neurons. Consequently, central terminals of primary afferents in the spinal dorsal horn experience depolarization upon activation of GABAA receptors (GABAAR). Thus, regulation of [Cl-]i in these terminals may significantly affect transmitter release. Determining the [Cl-]i changes in C-fiber terminals is pivotal to understand sensory processing. Methods: To image [Cl-]i we used the genetically-encoded ratiometric Cl- sensor, superclomeleon, using 2-photon microscopy on the acutely delaminated spinal cord in anesthetized mice. Superclomeleon was virally transduced selectively in C-fibers in NaV1.8-cre mice. The GABAAR agonist and antagonist muscimol and bicuculline, as well as the NKCC1 antagonist bumetanide, were used to modulate [Cl-]i in afferent terminals in the dorsal horn. Results: We found that [Cl-]i in C-fibers was higher in males than females. Bumetanide could decrease [Cl-]i in males but not in females. Bicuculline did not affect [Cl-]i in C-fibers in males but could increase [Cl-]i in females indicating the more important contribution of tonic GABAA signaling to [Cl-]i in Females. Conclusion: Presynaptic inhibition appears to be under distinct control by GABAergic inhibition between sexes, which should be taken into consideration in future studies.

P1-D-107: *Investigating the proliferative capacity of the inner ear blood-labyrinth barrier using in vitro organotypic explants*

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Sound transduction is driven by the stria vascularis (SV), a highly vascularized and specialized tissue which maintains the ionic environment within the cochlea. The SV also serves as the blood-labyrinth barrier, strictly controlling the movement of substances into the cochlea. Degeneration of the SV due to aging disrupts cochlear homeostasis, which results in progressive and significant hearing loss. However, there have been limited efforts to develop treatments for SV-related hearing loss. Therefore, we have developed an in vitro organotypic explant technique to investigate the properties of the SV. Using this method, we show that the neonatal SV is highly proliferative while the adult SV is not. We hypothesized that the SV loses the ability to proliferate with age by differential gene expression. Specifically, we examined the role of the Wnt/ß-catenin signalling pathway, which we have previously shown to play a significant proliferative role in cochlear cell types. We demonstrate here that pharmacological inhibition of Wnt/ß-catenin signalling in neonatal SV explants significantly reduces proliferation, which indicates that Wnt/ß-catenin signalling may be a key player in the proliferative capacity of the SV. We are currently investigating the effects of Wnt/ß-catenin activation in adult SV explants to determine whether we can promote proliferation in adult tissue.

P1-D-108: *ASK1 is a novel molecular target for preventing aminoglycoside induced sensory hair cell death*

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Aminoglycoside antibiotics are lifesaving medicines, crucial for the treatment of chronic or drug resistant infections. However, aminoglycoside-treated individuals can develop permanent hearing loss and vestibular impairment because aminoglycosides are toxic to the sensory hair cells in the inner ear. There is considerable evidence that reactive oxygen species (ROS) production and the subsequent phosphorylation of c-Jun N-terminal kinase (JNK) and P38 mitogen-activated protein kinase (P38) drives apoptosis in aminoglycoside-treated hair cells. However, treatment strategies that directly inhibit ROS, JNK or P38 are limited due to the importance of these proteins for normal cellular function. Alternatively, the upstream regulator apoptosis signal-regulating kinase 1 (ASK1/MAP3K5) is a key mediator of ROS-induced JNK and P38 activation under pathologic but not homeostatic conditions. We used cochlear explants from Ask1 knockout mice to investigate ASK1 as a mediator of drug-induced hair cell death, demonstrating that Ask1 deficiency attenuates neomycin-induced hair cell death. We then evaluated ASK1 inhibitor GS-444217 as a potential otoprotective therapy. Pharmacological inhibition of ASK1 significantly attenuated hair cell death in neomycin-treated explants but did not impact aminoglycoside efficacy against P. aeruginosa in the broth dilution test. Overall, we provide significant pre-clinical evidence that ASK1 inhibition is a novel strategy for preserving hearing and balance function by preventing aminoglycoside ototoxicity.

P1-D-109: *Neural circuit mechanisms of Drosophila larvae behavior elicited by an aversive odor*

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To successfully navigate these environments and survive, the nervous systems of animals must process massive sensory inputs and produce the appropriate actions. Olfaction, an evolutionarily ancient sense, allows almost every animal to perform behaviors crucial for survival, such as foraging for food and avoiding predators. As the circuitry and neurons of olfactory systems have been studied in detail, I am interested in the neural circuit mechanisms for behaviors guided by odors. The Drosophila larva is an excellent model system to study olfaction. Past studies have focused on behaviors elicited by attractive odors, but the circuit mechanisms underlying behaviors elicited by aversive odors remain unclear. The goals of this project will be to investigate the neural circuitry responsible for behavior elicited by aversive odors, and to identify the behavioral algorithm that regulates such behavior.

P1-D-110: *THE effect of Parkinson's disease on white matter integrity between olfactory and trigeminal brain areas*

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Olfactory dysfunction (OD) is a frequent symptom of Parkinson's disease (PD) that appears in early stages. Studies suggest that PD related OD is different from other forms of non-parkinsonian OD (NPOD; related to sinunasal disease, viral infection, trauma, etc.), as PD patients maintain trigeminal sensitivity while patients NPOD typically exhibit reduced trigeminal sensitivity. The difference in trigeminal sensitivity between the two types of patients leads to distinct imaging features. Indeed, in previous work, we identified a specific pattern of functional connectivity between olfactory and trigeminal chemosensory brain processing area in PD patients and in NPOD patients. Here, we aim to further understand these results by investigating white matter fiber integrity in PD patients and NPOD subjects. We hypothesized the presence of a specific alteration of white matter fibers between the chemosensory regions in PD compared to NPOD patients. Specifically, we aimed to assess potential differences in white matter fiber integrity between the chemosensory regions using diffusion MRI in 15 patients with PD and compare them to 15 patients with NPOD and to 15 controls. Group differences and similarities will be discussed in light of the existing literature. In summary, this study will provide a better understanding of PD-related OD with the aim of differentiating it from NPOD, an

important step towards the use of olfaction as an early marker and potentially as a screening tool for PD.

P1-D-111: *Altered hypothalamic structure in trigeminal neuralgia*

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Objectives: Pain and stress are two different processes with significant physiological overlaps. Chronic pain patients commonly experience increased anxiety and depression. In this study, we aim to investigate the hypothalamic changes in chronic pain using trigeminal neuralgia (TN) as our model. In this study, we investigated the hypothalamic subregions in TN patients compared to healthy controls (HC) and we hypothesize that the hypothalamic subregion volumes are statistically different compared to healthy controls. Methods: 3T T1 MRIs were retrospectively identified from 61 patients with classical TN and their respective age- and sex-matched HC from the Cam-CAN database. FreeSurfer 7.2 was leveraged to extract gray matter (GM) volume from the hypothalamus and its subunits. Welch's t-tests were used to compare corrected GM volume between TN patients and HC across hypothalamic subunits. Results: GM volumes of bilateral anterior superior and posterior subunits were markedly smaller in classical TN patients (age: 61.4 -14.0 s.d. years, 36 females and 25 males) compared to HC ($p < 0.01$). This is associated with a significant bilaterally smaller whole hypothalamus GM volume ($p< 0.001$). Sex subgroup analysis further revealed that the significantly smaller GM volume in classical TN patients was driven by females ($p < 0.05$), but not males. Additionally, sex-independent abnormalities in GM volume were observed in contralateral tubular superior subunit ($p < 0.05$) and ipsilateral tubular inferior subunit ($p < 0.05$) in TN patients compared to HC. Conclusion: Our study reports for the first-time hypothalamic subunit changes in chronic pain patients. Additionally, this study is another demonstration of significant sex differences in chronic pain-induced abnormalities in the brain.

P1-D-112: *Multiscale computer model of the spinal dorsal horn reveals changes in network processing associated with chronic pain*

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Pain-related sensory input is processed in the spinal dorsal horn (SDH) before being relayed to the brain. That processing profoundly influences whether tactile stimuli are correctly or incorrectly perceived as painful. Different types of excitatory and inhibitory neurons have been identified in the SDH, and some of their connectivity is understood, but how the overall circuit processes sensory input or how that processing is disrupted under chronic pain conditions remains unclear. To explore sensory processing in the SDH, we developed a computational model of the circuit that is tightly constrained by experimental data. Our model comprises conductance-based neuron models that reproduce the characteristic firing patterns of spinal neurons. Different spinal neuron populations were synaptically connected according to available qualitative data. Using a genetic algorithm, synaptic weights were optimized to reproduce projection neuron firing rates (model output) in response to primary afferent firing rates (model input) across a range of mechanical stimulus intensities. This optimization revealed that distinct synaptic weight combinations could produce equivalent SDH circuit function, revealing degeneracy that may underlie heterogeneous responses of different circuits to perturbations or pathological insults. To validate our model, we verified that it responded to reduction of inhibition (i.e. disinhibition) and ablation of specific neuron types in a manner consistent with experiments. Our validated model offers a valuable resource for interpreting experimental results and testing hypotheses in silico to plan experiments for examining normal and pathological SDH circuit function.

P1-D-113: *Towards rAAV-mediated CRISPR/Cas9 gene editing for congenital blindness aniridia*

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Aniridia is a rare congenital blindness with unmet therapeutic needs, which is caused by mutations in the Paired box 6 (PAX6) gene. Here we explored the possibility of using CRISPR-based gene editing as a therapy for aniridia. First, we improved the Pax6 small eye (Sey) mouse model, which carries a patient-specific mutation, by endogenously FLAG tagging the mutant allele, thereby allowing for the differential detection of protein from each allele. Second, we developed a CRISPR correction strategy in vitro, then tested it in vivo in the germline of our new mouse to validate the causality of Sey mutation prior to somatic gene therapy. Finally, we used a reporter system to identify the target of our recombinant adeno-associated viruses (rAAVs) in the aniridic eye. The genomic manipulations were analyzed by Sanger and next-generation sequencing. The mice were studied by slit lamp imaging and immunohistochemistry. We achieved both in vitro and in vivo germline correction of the Sey mutation, with the former resulting in an average 34.8% ± 4.6% SD correction, and the latter in restoration of FLAG-tagged PAX6 expression and normal eyes. We observed wide transduction of retinal and corneal cells at adulthood with direct-to-eye delivery of rAAVs. Hence, we have established a new mouse model for testing CRISPR-based therapies for aniridia, developed a robust CRISPR-based strategy for

correcting the Sey mutation, confirmed the causality of Sey mutation, and finally reported the success of our delivery methods for efficient targeting of retinal and corneal cells in aniridic mice.

P1-D-114: *Neuromuscular Junction re-innervation following injury is mediated by endocannabinoid CB1 Receptor*

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Peripheral nerves show a great regenerative ability following nerve injury. Not only changes along the damaged nerve occurred but also at the neuromuscular junction (NMJ), where degeneration/re-innervation processes occur in pathological and physiological conditions. Perisynaptic Schwann cells, glial cells at the NMJ, are important for NMJ's repair. Despite evidence for their roles in axonal guidance and synapse formation, Cannabinoids' involvement in nerve injury response remains ill defined. We observed that CB1 receptors are expressed in different muscles and are upregulated immediately after nerve crush. Daily treatment with the CB1 antagonist AM251 (IP injections, 3 mg/kg) during the period of re-innervation following nerve injury caused a downregulation of the CB1 expression and greatly limited re-innervation as indicated by a significant number of denervated NMJs ($p < 0.05$). In EDL muscles, the increased percentage of denervated NMJ was accompanied by a decrease of poly-innervation, likely due to a delay in the re-innervation process. Moreover, this CB1 regulation may be mediated by a c-Jun pathway since we observed a significant decrease of c-Jun expression ($p < 0.05$). These data highlight a novel role of CB1 receptor at NMJ and in the control of NMJ re-innervation after nerve injury. A better understanding of these mechanisms could help address the inadequate NMJ maintenance observed in motor neuron-related neurodegenerative diseases.

1E. Homeostatic and Neuroendocrine Systems

P1-E-115: *Impact of gestational hyperglycemia on the development of the rat fetal hypothalamic melanocortin system*

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Gestational Diabetes (GD) is associated with adverse metabolic outcomes in offspring, such as increased vulnerability to develop obesity and type 2 diabetes. Prior research has attributed obesity

and other metabolic disorders by a dysregulation of the melanocortin system. Indeed, it is possible that GD may influence the development of this system and confer this vulnerability. We employed an experimental model of GD to examine how a maternal hyperglycemic state impacts the development of this system in the arcuate nucleus (ARC) in the developing fetus. To do this, we induced a mild diabetic state by injecting intraperitoneally pregnant Wistar rats with a low dose of streptozotocin (STZ; a pancreatic beta cell toxin), inducing a mild hyperglycemic and insulin deficient state. The injection of vehicle or 35 mg/kg of STZ was given (N=8/group) one week after impregnation was confirmed. GD was confirmed with a glucose tolerance test on day 15 and following this confirmation, on day 19, pregnant females were deeply anesthetized, and their fetuses were extracted via c-section. Fetuses were rapidly decapitated, and their heads were immediately submerged in 4% paraformaldehyde for fixation. Sections from these brains containing the ARC were processed for immunohistochemistry detecting the pro-opiomelanocortin (POMC) peptides. Results showed that pups harvested from STZ-treated rats had lower number of ARC POMC stained cells, suggesting that maternal hyperglycemia may be influencing the development of the melanocortin system, conferring vulnerability to metabolic disorders.

P1-E-116: *Programming of hypothalamic and placental gene expression in a rat model of gestational diabetes*

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Gestational diabetes (GD) is a risk factor for offspring obesity and insulin resistance in adulthood. The hypothalamus is critical for regulating energy balance and its development begins during mid-gestation, continuing into early life. As such, it is possible that maternal metabolic state influences hypothalamic development. Also, the placenta is the main route by which maternal hyperglycemia affects the developing fetus. Here, we used a rat model of GD to determine how this altered metabolic state influences hypothalamic and placental gene expression to potentially program metabolic vulnerability. Pregnant rats were injected on pregnancy day 7 with 35mg/kg of streptozotocin (STZ) to induce maternal hyperglycemia. On gestational day 19, pregnant rats underwent caesarean section and fetal placentas, and brains were harvested and flash frozen. Hypothalami and the fetal placental zones were used for bulk RNAseq experiments to analyze changes in gene expression. Results show that in the placenta, gestational hyperglycemia caused an upregulation of collagen-related gene expression as well as downregulation of genes associated with oxidative phosphorylation (OxPhos). In the hypothalamus, an increase in glutamate-signalling gene expression as well as a reduction in antioxidant and OxPhos gene expression was observed in fetuses from STZ-treated rats. These data suggest that maternal hyperglycemia impacts processes associated with substrate utilization and

angiogenesis in the placenta, and those associated with oxidative stress and neuronal cell death in the hypothalamus.

P1-E-117: *Impacts of gestational bisphenol A exposure on adult hypothalamic neurogenesis*

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Regulation of physiological homeostasis by the hypothalamus is influenced by low basal levels of adult neurogenesis. Adult hypothalamic neurogenesis is involved in maintenance of energy balance and responds to energy homeostasis disruptions. Hormones such as oestradiol interact with changes in energy balance to alter rates of prenatal and adult neurogenesis, demonstrating sensitivity of hypothalamic neural progenitor cells to endogenous hormones. We previously showed that gestational exposure to the hormone mimic bisphenol A (BPA) accelerates embryonic hypothalamic neurogenesis with lasting effects on hypothalamic function. The present study investigates the impact of gestational BPA exposure on hypothalamic progenitors that contribute to adult neurogenesis and the interaction with energy balance disruptions via high-fat diet. Pregnant dams were fed a control diet or chow laced with a low dose of BPA (50 µg/kg diet), then offspring were placed on low-fat or high-fat diet throughout adolescence (postnatal day (P) 5-35) and weighed every 5 days. Intraperitoneal injections of BrdU were done twice daily from P45-53. To identify changes in the proliferating cell population as a result of gestational BPA exposure and energy balance changes, P54 and P75 brains were co-stained for BrdU and cell type specific markers. Results showed that BPA exposure altered weight gain in adolescent and adult female mice. Preliminary data demonstrate a trending increase in neurogenesis in P54 females exposed to BPA, suggesting BPA may have an estrogenic effect on hypothalamic neural progenitors.

P1-E-118: *Chronic Stress Increases Ghrelin Entry into the Arcuate Nucleus of the Hypothalamus*

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Ghrelin is a stomach-derived peptide hormone that increases food intake through central activation of the growth hormone secretagogue receptor (GHSR). Circulating ghrelin levels also rise in response to stressors and plays an important role in the regulation of feeding behavior and metabolism in the face of stress. The mechanisms by which ghrelin regulates such behaviors is still being elucidated, as ghrelin movement into and throughout the brain is extremely limited by the blood brain barrier. Notably, social stressors have been found to increase blood brain barrier permeability and therefore

may increase the ability of large peptide hormones, like ghrelin, to enter the brain. To investigate if stress influences blood brain barrier permeability to ghrelin, male mice were subjected to 21-days of chronic social defeat stress then subcutaneously injected with 300pmol/g of fluorescently labelled ghrelin, Cy5-ghrelin. Mice were then sacrificed 7-, 15-, 30-, or 60-minutes following injection, to monitor ghrelin movement throughout the brain. The results showed that stress exposure increased Cy5-ghrelin fluorescence in the arcuate nucleus of the hypothalamus, compared to non-stressed controls. Despite increased ghrelin accumulation in regions adjacent to the ventricles, stressed mice showed no change to ghrelin infiltration into other brain regions. Overall, the results suggest that increased food intake during stress may be facilitated by the increased ghrelin accumulation in the arcuate nucleus.

P1-E-119: *Functional role of NaX channels in the magnocellular neurosecretory cells of the supraoptic nucleus of rats*

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Body fluids are continuously monitored to regulate the electrolyte-water balance. The central monitoring of this process occurs at the circumventricular organs which lack blood-brain-barrier. Neurons in these structures are in contact with peripheral blood and cerebrospinal fluid, and they project to the magnocellular neurosecretory cells (MNCs) in the supraoptic (SON) and paraventricular nuclei (PVN). We hypothesized that MNCs can detect the extracellular sodium concentration ([Na+]o) through the sodium channel NaX. Although this channel is somewhat homologous to voltage-gated sodium channels (VGSCs), it differs from the other family members, including in key regions for voltage sensing and inactivation. Moreover, NaX channels are tetrodotoxin-resistant. In the present work, we demonstrated that both vasopressin and oxytocin, MNCs express NaX channels. Functionally, MNCs respond to a hypernatremic-isoosmotic stimulus with a depolarisation that increases their firing rate. This depolarisation temporally correlates with an inward current whose reversal potential corresponds to the equilibrium potential for sodium. In addition, the NaX current magnitude was dependent of the [Na+]o . The NaX current was isolated by blocking other sodium permeability pathways that are present in MNCs, such as VGSCs, epithelial sodium channels (ENaCs) and TRPV1 channels. Finally, we demonstrated that virally-mediated knockdown of NaX channels in MNCs reduced their electrophysiological response to physiological stimulus (hyperosmotic-hypernatremic) in vitro, as well as the sodium-mediated increase in c-fos expression in vivo. These data suggest a functional role for NaX channels in sodium detection by MNCs.

P1-E-120: *Neuronal Adipose Triglyceride Lipase (ATGL) regulates peripheral metabolism in an evolutionary conserved and sex-specific manner.*

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Adipose Triglyceride Lipase (ATGL) catalyzes the first step in triglyceride hydrolysis, and plays a major role in regulating energy homeostasis in peripheral tissues. ATGL is also expressed in the brain, including in AgRP neurons of the arcuate nucleus (ARC) that play key role in energy homeostasis. The physiological significance of brain ATGL remains unclear. We found that ATGL regulates lipid droplet content in cultured neurons, similar to peripheral cells. ATGL expression in the ARC is upregulated by cold exposure and fasting, suggesting ATGL plays a role in adaptive responses to metabolic challenges. Indeed, genetic knockdown of neuronal ATGL in C.elegans and D.melanogaster increased peripheral fat and reduced fasting-induced lipolysis. This suggests a conserved mechanism whereby neuronal ATGL promotes lipolysis in peripheral cells. Supporting this, ATGL knock-out specifically in ARC neurons affects energy expenditure, meal pattern and thermoregulatory responses to cold in chow fed male mice without affecting body weight gain. These changes were not observed in female mice, suggesting male-specific regulation of energy balance by neuronal ATGL, similar to findings in flies. Ongoing studies show changes in fat distribution and glucose homeostasis in mice with a specific ATGL knockout in AgRP neurons, suggesting this neuronal subpopulation is involved in the control of energy homeostasis by ATGL. Taken together, our findings reveal a previously unrecognized role for neuronal ATGL in regulating whole-body energy homeostasis.

1F. Cognition and Behavior

P1-F-121: *Effects of a chronic social defeat stressor on behavior and GABAA receptor α subunits in the gut-brain axis*

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Gamma-aminobutyric acid type A receptors (GABAAR) have been involved in depression and anxiety. Probiotics with established antidepressant- and anxiolytic-like properties mainly belong to bacterial genera capable of producing GABA, which are reduced in depression and anxiety. Their mechanisms of action remain to be determined. This study examined behavior and GABAAR α subunits expression in the gut-brain axis in a mouse model of depression. A second aim investigated the viability of a bacterium harboring the gene coding for glutamate decarboxylase beta (gadb), an enzyme converting glutamate to GABA. Male C57BL/6N mice were gavaged for 14 days with a bacterium containing gadb or with phosphate-buffered saline (PBS). PBS-treated mice were then exposed to chronic social defeat or a control condition, after which behavior was assessed during 3 days and brain/intestinal samples were collected for GABAAR α subunits determination. Intestinal viability of the bacterium was examined via bioluminescence imaging. Mice susceptible to the behavioral effects of the stressor were hypoactive in the social interaction and the light-dark tests. Although GABAAR α subunits were unchanged by the stressor, their cohesion in the prefrontal cortex was higher in susceptible mice than in non-stressed mice. After surviving intestinal transit, the bacterium with gadb was detected 24h after gavage. The behavioral and GABAAR α subunits profiles reported will be used to examine the effects of GABA-producing bacteria on behavior via their effects on GABAAR α subunits cohesion in the gut-brain-axis.

P1-F-122: *The role of dopamine in expression of occasion setting by a positive or negative feature morphine drug state*

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Background: One aspect of opioid use disorder is the elicitation of behaviours by drug cues. Interoceptive drug cues may modulate behavioural responsivity to exteroceptive drug cues through Pavlovian conditioning. To model this effect in rats, a drug state may be trained as a feature positive (FP) or feature negative (FN) occasion setter (OS) to disambiguate the relationship between a discrete conditioned stimulus (CS) and an unconditioned stimulus. Dopamine has been implicated in cued reward seeking, so we aim to investigate its role in the functioning of a morphine drug state as a FP or FN OS. Methods: Male and female rats were assigned to FP or FN training groups and received daily intermixed morphine or saline injections before training sessions. Training sessions consisted of presentations of a white noise CS followed by access to sucrose on morphine, but not saline sessions, for FP rats. FN rats learned the reverse contingency. Following acquisition, rats were tested for morphine discrimination after systemic pretreatment with the non-selective dopamine receptor antagonist flupenthixol, the non-selective dopamine receptor agonist apomorphine, or saline vehicle. Results: Male and female FP and FN rats acquired the discrimination. At this stage, flupenthixol and apomorphine appear to inhibit sucrose seeking on test trials in all rats in a dose- and sex-dependent

manner, likely through distinct mechanisms. Conclusion: Our findings thus far may lend support to a mechanism of OS involving gating of CS-induced dopamine release by FP or FN drug states.

P1-F-123: *Network changes preceding behavioural changes during impaired memory formation*

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Retinoic acid is the active metabolite of vitamin A, and deficits in retinoid signaling can impair vertebrate learning and memory. Retinoic acid is also required for normal memory formation following operant conditioning of the respiratory behaviour of L. stagnalis. Here, we utilized electrophysiological recordings to simultaneously assess both behavioral and network parameters in semi-intact animals, either directly after training or after long-term memory formation. An inhibitor of retinoic acid synthesis, citral, was used to impair retinoid signaling in one group of trained animals. Citral treatment of these trained animals had no impact on learning, but impaired long-term memory formation at 24 hrs. However, despite no deficits in learning behaviour, key neuronal and network properties of these citral-treated trained animals were different from the vehicle-treated trained animals, and more closely resembled those of naïve animals. These same network properties continued to differ in the citral-treated animals that exhibited impaired memory formation 24 hrs later. Inhibiting RA signaling thus led to differences in the respiratory motorneurons and central pattern generator (CPG) immediately after training, though deficits in behaviour were not observed until the following day. These findings shed light on how deficits in RA signaling influence network properties and indicate that key changes in the CPG network precede behavioral deficits.

P1-F-124: *ERP evidence of hyperexcited cortical responses to the visual stimuli in migraine headache disorders*

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New findings from migraine studies have indicated that this common headache disorder is associated with anomalies in attentional processing. In tandem with the previous explorations, this study will provide evidence to show that visual attention is impacted by migraine headache disorders. 43 individuals were initially employed in the migraine group and 33 people with non-migraine headache disorders were in the control group. The event-related potentials (ERP) of the participants were calculated using data from a visual oddball paradigm task. By analyzing the N200 and P300 ERP components, migraineurs, as compared to controls, had an exaggerated oddball response showing

increased amplitude in N200 and P300 difference scores for the oddball vs. standard, while the latencies of the two components remained the same in the migraine and control groups. We further explored these components in the two types of our migraine population (with and without aura) and the non-migraine headache controls. One-Way ANOVA analysis of the two migraine groups and the non-migraine control group showed that the difference level of N200 and P300 amplitude mean scores was greater between migraineurs without aura and the control group while these components' latency remained the same relatively in the three groups. These results give more neurophysiological support that people with migraine headaches have altered processing of visual attention.

P1-F-125: *Revelation of NfkB-P38 MAPK signaling in streptozotocin-induced diabetes-associated cognitive decline*

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It has been evinced that streptozotocin (STZ) induced intracellular glucose following neurochemical and structural abnormalities are the leading causes of neuronal damage consequently learning and memory deficits. Chebulinic acid (ChA), a flavonoid isolated from Terminalia Chebula, has potent protective effects on peripheral and central streptozotocin (STZ)-induced diabetic and diabetic connected AD. Recently, the effects of ChA on learning and memory concerts were monitored in many animal models of perceptive impairment. However, to date, no studies have investigated the ameliorative effects of ChA on diabetes associated with cognitive decline (DACD). In this study, we examined the effects of ChA, using a STZ-treated rat model and explored its potential mechanism. Diabetic rats were treated with ChA (25, 50 and 100 mg/kg/i.p) for 14 days. The learning and reminiscence function were assessed by Morris water maze test. The oxidative stress markers malondialdehyde (MDA), nitrite (NO) and GSH (glutathione) and inflammatory cytokines (TNF-a, IL-1β, and IL-6) were measured in hippocampus. P38 MPAK was evaluated using Elisa. The results showed that ChA supplement in STZ administered rats amended learning and memory performances compared with the STZ group. Additionally, ChA complement GSH levels, reduced MDA and NO levels, and alleviated TNF-α, IL-1β, and IL-6 compared with the STZ group in the hippocampus. The post-treatment with ChA also pointedly decreased NfκB-P38 MAPK expression. Our results showed that ChA may be a promising appropriate agent for improving cognitive decline in DACD.

P1-F-126: *Visual perception in hearing ASL signers*

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Deaf sign language users are better at some visual tasks compared to hearing individuals with no sign language experience, especially recognizing faces and detecting motion in the visual periphery. In the absence of auditory input, these enhancements are thought to reflect the increased importance of visual information for D/deaf individuals. Compared to spoken language, using a visual-manual language such as American Sign Language (ASL) also provides a drastically different visual experience. Therefore, it remains difficult to determine whether the visual enhancements observed in Deaf signers are the result of sign language experience or a direct consequence of hearing loss. The aim of the current study was to disentangle the effects of sign language experience and hearing loss by examining visual abilities in sign language users with typical hearing. Hearing signers and non-signers completed online assessments of their face matching and motion discrimination abilities in the central and peripheral visual fields. Additionally, hearing signers completed an online ASL proficiency test, which allowed us to examine the relationship between performance on the visual tasks and sign language skill. Hearing signers and non-signers performed similarly on the visual tasks, suggesting that the visual enhancements previously observed in Deaf signers reflect the role of hearing loss itself rather than sign language experience. We propose that differences in auditory experience from a young age result in distinct developmental paths and outcomes for Deaf and hearing signers and that exploring different aspects of sign language experience is important to understanding how it interacts with hearing loss.

P1-F-127: *Housing Density and Tank Size Affect Behavioural Responses in Adult Zebrafish*

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The zebrafish (Danio rerio) is a highly utilized laboratory model in a variety of biology studies, due in part to its robust, well documented behavioral repertoire and evolutionary conserved features, representing good translational relevance. The current industry standard of housing large numbers of fish in small tank volumes on commercial laboratory rack systems only considers maximal egg production and ignores the potential damaging effects of physiological and psychological stress due to crowding. Recent sporadic reports have suggested that this standard of housing zebrafish is unnatural and suboptimal, negatively impacting a variety of phenotypes. Thus, we have conducted the first systemic proof of concept analysis examining the impact of housing density and tank size on the behavioural responses of zebrafish. Zebrafish were randomly assigned to one of three tank volumes (1.5L, 10L, and 50L) with one of three housing densities (1, 2, and 4 fish/L) for 2 weeks, a 3x3 between subject experimental design. Fish were singly placed in an experimental tank where they were presented with shoaling (conspecifics) stimulus and stimulus mimicking an approaching predator. Numerous swim path parameters of the zebrafish were recorded and quantified using Ethovision tracking software. Significant behavior specific effects of the employed housing conditions

were found. Average speed and variance of speed, average turn angle and variance of turn angle, average distance to stimulus side, average distance to bottom and duration of high mobility were all affected. These results suggest that both tank size and housing density may exert significant negative effects on behaviour, and thus should be considered in zebrafish husbandry.

P1-F-128: *The herbal alkaloid Rhynchophylline modifies sleep and the brain spatial transcriptome in mice*

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Herbal medicines containing the alkaloid rhynchophylline (RHY) increase sleep duration and quality in humans. Although treatment with RHY alone has not been tested in humans, rodent studies suggest that it modulates cellular pathways involved in sleep/wake regulation by targeting ion channels, receptors and kinases. We thus studied RHY effects on sleep and related molecular mechanisms. The electrocorticogram was recorded in male and female mice receiving 50 or 100 mg/kg of RHY (or saline) at light onset and 1h before light offset. Sleep architecture and spectral activity were examined. Additional groups had their brain sampled 3h after each injection to assess changes in the spatial transcriptome. In both sexes, but to a larger extent in females, RHY decreases wake and increases slow wave sleep (SWS) during the dark period, and reduces paradoxical sleep (PS) in the light period. Moreover, RHY shortens individual bouts of wake and SWS. RHY also reduces α (8-12Hz) activity in wake and modifies the time-course of SWS delta (1-4Hz) and sigma (10-13Hz) activity. Male and female brain transcriptome reveals that RHY modifies the expression of some genes throughout the brain (e.g., Sgk1, Arl4d, Cdkn1a, Tmem252, Lcn2, Uba52), while the expression of other transcripts linked to sleep regulation and pituitary functions (Pmch, Hcrt, Gh, Oxt, Pomc) is specifically decreased in the hypothalamus. Gene expression findings identified underlying RHY mechanisms involving wake/sleep regulatory circuits, and highlight the complexity of the brain transcriptomic response to sleep-inducing drugs.

P1-F-129: *Chronic stress-induced anhedonia-like behavior can be mimicked by cortical astroglial ablation and reversed by increased astroglial activity*

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Astroglia loss and decreased expression of specific markers expressed by GFAP (glial fibrillary acidic protein)-astroglia have been found in key brain regions such as the prefrontal cortex (PFC) in MDD patients and rodent chronic stress models. In this study, we examined the consequences of PFC GFAP-astroglia ablation on depressive-like behaviours and potential reversal of chronic stress-induced deficits by enhancing PFC GFAP-astroglia activity. GFAP-cre mice infused in the PFC with an AAV5-DOI-CMV-DTR (diphtheria toxin (DT) receptor) were behaviourally assessed following i.p. injection with DT in several tests measuring anhedonia- and anxiety-like behaviors. We found that PFC astroglial ablation induced significant anhedonia- but not anxiety-like deficits. We also infused wild-type mice with an AAV5-GFAP-DREADD(designer receptor exclusively activated by designer drug)Gq in the PFC to activate GFAP-astrocytes upon clozapine-N-oxide administration. While PFC GFAP activation had no effects at baseline (no stress condition), it reversed the anhedonia-like deficits induced by chronic stress exposure. No reversal of anxiety deficits was observed. Current work focuses on validating increased astroglia activity using Ca2 fiberphotometry and deltaFos staining. Our results demonstrate that cortical GFAP-astroglia loss is sufficient to induce anhedonia and that chronic stress-induced anhedonia-like deficits can be reversed by increased GFAP-astroglia activity. Altogether, our work suggests a critical role of astroglia in the expression and the treatment of key symptoms of MDD.

P1-F-130: *Anatomy of raphe to hippocampus glutamatergic projections and contribution to sharp wave ripples modulation*

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A key role of the hippocampus is memory consolidation. Hippocampal sharp wave ripples (SWR) are brief, high frequency oscillations (~50 ms, 150-250 Hz) present during slow wave sleep that directly contribute to this function. The median raphe is known to modulate hippocampal rhythms and contains a glutamatergic long-range projecting population, characterized by the expression of type 3 vesicular glutamate transporter (VGLUT3), whose functions remain largely unexplored. In this study, we aim to provide an anatomical characterization of this raphe-hippocampus glutamatergic pathway and investigate its contribution to SWR activity. First, using a combination of CRE-dependent retrograde viral vectors and VGLUT3-CRE mice we identified hippocampus-projecting glutamatergic neurons within the raphe nuclei. We observed distinct glutamatergic pathways targeting the dorsal and ventral part of hippocampus and mainly unilateral projections. Second, we explored the contribution of glutamatergic neurons to SWR modulation. Electrophysiological recordings in the dorsal hippocampus of freely behaving mice during optogenetic activation of glutamatergic raphe neurons led to strong inhibition of SWR activity. Control experiments showed no effect of light delivery in the raphe on SWR. Our results suggest that glutamatergic inputs from the raphe modulate

hippocampus sub-regions and associated functions independently. In addition, we reveal a powerful inhibitory control of SWR through raphe glutamatergic neurons, suggesting a strong impact of this pathway on memory consolidation.

P1-F-131: *Dissociating the involvement of cholinergic muscarinic and nicotinic receptors in destabilization of object memories in male and female mice.*

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The content of long-term memory is neither fixed nor permanent. Reminder cues can destabilize consolidated memories, rendering them amenable to change before being reconsolidated. Reactivation-induced memory destabilization is thought to reflect a mechanism through which long-term memories can be adaptively maintained over time. However, not all memories destabilize following reactivation. Characteristics of a memory, such as its age or strength, impose boundaries on destabilization. Previously, we demonstrated that presentation of salient novel information at the time of reactivation can readily destabilize resistant object memories in rats and this form of novelty-induced destabilization is dependent upon acetylcholine (ACh) activity at muscarinic receptors. Until now, research has largely focused on muscarinic receptors, and little is known about the role of nicotinic receptors in memory destabilization. In the present study, we sought to determine the involvement of muscarinic and nicotinic receptors for the destabilization of both recent and remote object memories in male and female mice. Systemic (ip) administration of scopolamine (0.3 mg/kg) or mecamylamine (1.0 mg/kg) - muscarinic and nicotinic receptor antagonists, respectively - prevented destabilization of recent object memories, but only scopolamine did so for remote object memories. These results further highlight the importance of the muscarinic receptor pathway through which ACh mediates destabilization of resistant memories and, for the first time, demonstrate that this mechanism is also present in females. Funded by NSERC.

P1-F-132: *Neuroligin-2 modulates individual slow wave parameters and the response to sleep deprivation*

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Synaptic adhesion proteins modulate vigilance states, possibly via their involvement in neurodevelopment and neuroplasticity. Neuroligin-2 (NLGN2) is an adhesion protein expressed at the GABAergic synapse, and GABA plays multiple roles in sleep/wake regulation. Our group has shown

that, under baseline (BL) conditions, the knockout (KO) of Nlgn2 in male mice reduces the overall time spent asleep and increases absolute delta activity (1-4 Hz) during slow-wave sleep (SWS). We here aimed to understand whether specific parameters (e.g., amplitude, density) of individual slow wave (0.5-4 Hz) could explain this delta activity increase. We also aimed to verify the response of Nlgn2 KO mice to sleep deprivation (SD). Adult male Nlgn2 KO mice underwent surgical implantation of electrodes for electrocorticography (ECoG). The ECoG was recorded during 24h of BL, 6h of sleep deprivation (SD), and 18h of recovery. Nlgn2 KO mice showed an increased density, amplitude and slope of individual slow waves during BL and after SD. KO mice were also more difficult to keep awake during SD, and spent more time in SWS during the first 6h following SD. This was accompanied by an accelerated PS recovery. Furthermore, Nlgn2 KO mice showed an impaired response to SD for ECoG activity quantified during wake and PS. Our data support an implication of NLGN2 in the regulation of individual slow wave parameters and the response to sleep loss.

P1-F-133: *Medial prefrontal cortex routes relevancy of ongoing events to the nucleus reuniens*

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The medial prefrontal cortex (mPFC) and hippocampus (HPC) work concertedly during the consolidation and retrieval of event memories; however, their interaction during encoding remains unclear. Using a HPC-dependent memory task, we have shown that the mPFC changes its network activity patterns depending on whether a stimulus is predictive of an upcoming aversive event. Moreover, augmenting this relevancy-selective activity facilitated associative memory formation. Presently, we tested if this relevancy signal is routed to the HPC via the nucleus reuniens (RE), a structure reciprocally connected to both regions, and compared it to the mediodorsal thalamus (MD), a structure lacking direct HPC connectivity. We recorded mPFC axon terminal calcium activity in the RE and MD of rats undergoing differential trace eyeblink conditioning (DC), wherein only one of two conditioned stimuli (tone or light; CS+) was paired with a mild eyelid shock, whilst the other was presented alone (CS-). Prior to DC both CSs evoked large responses from mPFC axons in the MD, but not RE. During DC, mPFC axons in both the RE and MD showed larger responses to the CS+ than the CS-. Axons in the RE also showed increasing responses to the CS+ across days, a trait not seen in axons within the MD. Once rats formed the CS+ shock association, the CS+ evoked much stronger responses from axons in the RE compared to those in the MD. These results suggest that the mPFC preferentially routes the mnemonic qualities of a stimulus to the RE. Such a relevancy signal may in turn govern encoding of these stimuli in the HPC.

P1-F-134: *Investigation of the role of DCC-positive neurons in adult prefrontal cortex in susceptibility to social defeat stress*

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Elevated expression of the guidance cue receptor gene, DCC, in the adult prefrontal cortex (PFC) is a hallmark of major depressive disorder. DCC receptors regulate neuronal connectivity and plasticity in adulthood, by orchestrating dendritic arborization and synapse formation. In adult mice, downregulation of Dcc levels in the PFC promotes resilience to chronic social defeat stress (CSDS), indicating a causal link, but the underlying mechanisms are not known. Here we evaluated whether DCC receptors play a role in stress susceptibility by altering dendritic architecture of selective PFC pyramidal neuronal projections. Using a retrograde neuronal tracer in adult mice, we determined that DCC-positive neurons in prelimbic and infralimbic PFC subregions innervate predominantly the nucleus accumbens (NAc) core and shell, compared to basolateral amygdala (BLA) projections. Next, we assessed the effects of CSDS on dendritic spine density and morphology in DCC-positive pyramidal neurons projecting to the NAc Shell. Compared to control and resilient mice, susceptible mice show reduced thin and/or mushroom spine density in apical, but not basal dendrites in DCC-positive neurons in prelimbic and infralimbic subregions, suggesting loss of both new and mature spines. Deleting Dcc in NAc Shell neuronal inputs, including PFC projections, induces resilience to CSDS. These findings suggest that DCC receptors in the adult PFC play a causal role in susceptibility to chronic social stress by altering the architecture of selective corticolimbic circuits.

P1-F-135: *The effect of rearing in a shelved environment on behavioral and physiological markers of welfare*

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Early-life experiences are critical modifiers of development. An important component of early life experience is the nature of maternal interactions, which can be modified by stress. During rearing, mothers are typically allocated to single level cages where they are readily accessible to pups, a potentially stressful scenario not reflective of nature. Accordingly, mothers regularly removed from the rearing environment interact differently with their offspring, leading to long-term changes in offspring physiology and behavior, particularly as it relates to stress. Commonly, modifications occur within the stress-axis, of which corticosterone is a major component. Corticosterone can be measured relatively non-invasively in rats via several methods including feces. Modifications in the stress-axis may also be manifested through changes in affective behavior and assessed via the open field,

elevated plus maze and in-cage behaviors. Additionally, tests of affect can be coupled with ultrasonic vocalization (USV) analysis, a method of assessing animal welfare on a continuous basis. Reducing mother stress during the rearing period may be a critical factor in determining the developmental trajectory of offspring. Thus, we allocated mothers to standard single level cages or cages with an integrated shelf and performed multiple physiological and behavioral assays related to stress as a means of determining shelf impact on offspring development. Offspring reared in standard cages weighed more, and had reduced anxiety, as determined by behavior in the open field. Improving welfare for dams can have a lasting impact on offspring that may complicate between lab comparison.

P1-F-136: *Contextual novelty or activation of M1 muscarinic cholinergic receptors promotes spatial memory destabilization in aged mice*

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Previously consolidated memories can be reactivated by exposure to reminder cues. This can destabilize memories, enabling weakening, strengthening, or information integration. Following this, memories need to be reconsolidated. The age and strength of a memory can affect its likelihood to destabilize, and exposure to novelty or activation of M1 muscarinic cholinergic receptors (mAChRs) at the time of reactivation can promote memory destabilization. Here, we show that in young male C57BL/6 mice, strongly encoded object location (OL) memories do not readily destabilize, but destabilization can be initiated by exposure to contextual novelty during memory reactivation. Moreover, both standard destabilization of weak OL memories, and novelty-induced destabilization of strong OL memories are prevented by mAChR antagonism with systemic scopolamine (0.3 mg/kg). In addition, activation of M1 mAChRs with systemic CDD-0102A (0.3 mg/kg) facilitated destabilization of strongly encoded OL memories without the presence of novelty during memory reactivation. Interestingly, unlike in younger mice, weakly encoded OL memories did not readily destabilize in nine-month-old mice, but destabilization could be promoted by exposure to novelty during memory reactivation or activation of M1 mAChRs. This research enhances our understanding of the role of acetylcholine in long-term memory dynamics and suggests implications for the understanding and treatment of cognitive inflexibility that can occur in the normal aging process as well as dementia.

P1-F-137: *Prefrontal ensemble dynamics during inference of adaptive action*

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The medial prefrontal cortex (mPFC) extracts common patterns across various experiences to support the prediction of the most adaptive behaviour in new situations. However, the underlying neuronal ensemble properties by which the mPFC performs this transformation remains unknown. To address this, we monitored spiking activity in the prelimbic region of the mPFC while rats inferred a new goal-directed behaviour - without any explicit training - by transforming previous learned stimulus-outcome-context relationships. Rats underwent a differential associative learning task in an environment consisting of two boxes connected by a short central alley. In each box, one of two neutral stimuli (CS; tone or light) signaled imminent shock to the eyelid (US). After rats successfully learned the CS-context relationships, they underwent a test session in which we removed the divider separating the two boxes for the first time. This environmental change enabled rats to avoid the US if they shuttled to the room in which the CS had not been paired with the US during the initial training stage. Rats that underwent this prior learning performed better on the test than did naïve rats that had no previous training. Using a network-level decoding approach, we found that the mPFC showed higher reactivation of the previously learned relationships immediately before rats performed the newly inferred adaptive action than when they performed an equivalent non-adaptive behaviour. Our results uncover real-time neuronal dynamics by which the mPFC transforms learned patterns to new adaptive behaviours.

P1-F-138: *Optimization and ontogeny of object-place recognition memory tasks in mice*

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Spontaneous recognition tasks are used to assess the what, where and when components of recognition memory. They have become widely used for assessing cognitive function in rodents due to their ease in not requiring prior training/motivational incentives. The object-place recognition task tests the ability to associate an object location with its identity. This behavioural task is commonly used to characterize cognitive deficits in rat models of neurodevelopmental disorders such as schizophrenia and autism spectrum disorders. Importantly, although these disorders have their clinical onset in early childhood, the object-place task has not been adapted for use in young rodents. While most object-place studies use adult rats, the genetic toolbox available in mouse models offers a valuable resource in the study of the etiology of neurodevelopmental disorders. This study sought to optimize the use of the object-place recognition task in mice across ages. We tested multiple variations of the object-place task which included testing with 4-objects, 2-objects, and varying number of training sessions. We found that a 2-object paradigm effectively probes object-place memory in C57 and C57/129J mice. We determined that the onset of object-place memory takes place between P25 and P28 in C57/129J mice. Optimizing behavioural tasks in mice that allow for testing during early life will yield a better understanding of the development of different memory types and

provide the necessary foundation for the use of these tasks at clinically relevant time points in animal models of disease.

P1-F-139: *Postural adjustments in cats during a reaching task reflect strategies to predict the forthcoming target location*

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Many types of movement depend on the production of appropriate postural adjustments in anticipation of an intended movement. As in most situations, such anticipatory postural adjustments (APAs) are influenced by learning and therefore subject to prediction strategies developed through learning. However, few studies have addressed how such prediction strategies affect APAs. To address this issue, we trained two cats on a reaching task in which the location of the target was predictable through learning. At the beginning of each trial, the cat maintained a standing position for several hundred milliseconds with each paw on a force plate. The target then appeared on either side of a touch panel that was placed horizontally in front of the cat. The target onset served as a 'Go' signal that instructed the cat to lift either forepaw to reach the target. A food reward was given immediately after the target was captured. The location of the target was switched between the left and right sides of the touch panel every three rewarded trials; the first of these trials was termed SWITCH trial and the other two were STAY trials. We found that in both cats APAs prior to target onset in STAY trials significantly depended on the predetermined target location. In SWITCH trials, while one cat exhibited APAs that were like those in the following STAY trials, the other showed APAs almost no different from those in the previous STAY trials. These results reveal that the two cats used different strategies according to whether the switching was predicted or not.

P1-F-140: *Phasic cholinergic modulation of the medial prefrontal cortex during probabilistic spatial learning*

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Basal forebrain (BF) cholinergic neurons are the primary source of acetylcholine in the cortex and are thought to modulate cortical activity and plasticity slowly. However, recent findings suggest that these neurons transiently increase firings in response to innately aversive stimuli (threat) with millisecond precision. The present study investigated the functional relevance of the threat-locked phasic cholinergic signaling by optogenetically manipulating it in one of BF efferent targets, the medial

prefrontal cortex (mPFC), in mice. To incorporate diverse mPFC-dependent cognitive processes in a single task, we developed a probabilistic spatial learning task where mice received probabilistic delivery of air-puffs midway when traversed one of two paths on a square-shaped track. When air-puffs were delivered 25% of the time in one path and 75% in the other, mice learned to slow down near the puff delivery zone and preferentially choose the path associated with the lower puff probability. When mPFC cholinergic terminals were optogenetically stimulated during air-puffs, mice chose two paths randomly while still decelerating toward the puff zone in both paths. In contrast, the same manipulation did not affect adaptive path selection or running speed when air-puffs were always delivered in one path but never in the other path. These results suggest that threat-evoked phasic cholinergic signaling modulates evaluation of threat uncertainty but not learning of threat location.

P1-F-141: *Alpha5 GABAA Receptor Positive Allosteric Modulation Improves Cognitive Performance in a Model of Unpredictable Chronic Mild Stress*

Ashley Bernardo[1], Michael Marcotte[1], Nathaniel Linga[2], Yeunus Mian[3], Sepideh Rezvanian[3], Dishary Sharmin[3], James Cook[3], Etienne Sibille[4], Thomas Prevot[1]

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Chronic stress is a risk factor for neurodegenerative disorders such as Alzheimer's Disease (AD) and is linked to reduced cognitive performance and neuronal atrophy. In both states, the GABAergic system shows reduced neuron populations, less GABA release and altered GABAA receptor (GABAAR) functioning. GABAAR's containing the α5 subunit are linked to cognition. GABAergic somatostatin neurons synapsing onto α5-GABAARs have reduced function in disease and stress states therefore no longer able to coordinate signals, presenting as cognitive impairments. With α5-GABAAR positive allosteric modulation (α5-PAM) there is potential to reintroduce signal coordination and improve cognitive performance. This study tested an α5-PAM in the unpredictable chronic mild stress (UCMS) mouse model (50% female; N=36/per study). We tested acute and chronic α5-PAM administration in a battery of cognitive tests: Y-maze (spatial working memory), Morris Water Maze (spatial learning and recall memory) and Cognition Wall (discrimination learning and cognitive flexibility). We found UCMS impaired spatial working memory, recall memory and discrimination learning. Acute administration of α5-PAM improved spatial working memory and discrimination learning while recall memory required chronic administration to see an effect. Molecular studies showed neurotrophic effects of α5-PAM. Overall, results support using α5-PAM to overcome chronic stress-induced cognitive impairments across several cognitive domains and has potential neurotrophic benefits that could support its use in disorders such as AD.

P1-F-142: *Investigating the role of M1 muscarinic receptors in object memory updating deficits in aging male mice*

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Age-related cholinergic system dysfunction disrupts many aspects of cognition, but its role in memory updating deficits has not been investigated. However, there is evidence that the cholinergic system is important for object memory updating. In young rats, M1 muscarinic acetylcholine receptor (mAChR) activation in perirhinal cortex (PRh) promotes object memory destabilization. M1 mAChR functioning in PRh is similarly required for reactivation-based object memory updating. We hypothesize that cholinergic dysfunction underlies age-related object memory updating deficits and that increasing M1 mAChR activation can restore these deficits. To test this, we used a post-reactivation object memory modification (PROMM) task for mice, in which reactivated object memory is updated with new contextual information. First, we characterized object memory updating abilities in mice at different ages; 3-month-old mice showed intact object memory updating, while 12-month-old mice were impaired. In young mice, blocking M1 mAChR activation systemically with dicyclomine (16 mg/kg) pre-reactivation prevented object memory updating. In aged mice, activating M1 mAChRs with CDD0102A (0.3 mg/kg) pre-reactivation improved object memory updating. Western blot analysis revealed increased M1 mAChR expression in PRh in aged compared to young mice. However, greater M1 mAChR levels in PRh were correlated with better PROMM task performance in young mice only. These findings suggest that altered cholinergic transmission in aging contributes to memory inflexibility.

P1-F-143: *Type 1 diabetes mediated increased capillary stalling and impaired behavioral performance in mice*

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Introduction Recent work from our lab has shown that the brain capillaries routinely get clogged by cells and debris even under healthy conditions. The present study was undertaken to determine how type 1 diabetes mellitus (T1DM) affects this phenomenon. Methods Both male and female C57BL/6 mice were injected with streptozotocin to induce T1DM. These mice were implanted with cranial windows and cortical volumes were imaged repeatedly from 3-9 weeks after induction of diabetes. To model susceptibilities to short or long lived obstructions, we injected (i.v.) 5µm diameter fluorescent microspheres in diabetic and control mice at 30 minutes and 3 days before euthanasia. To determine the impact of diabetes on cognitive and sensorimotor activity, mice were subjected to a battery of

behavioural tests. Results 2-photon imaging showed that diabetic mice have higher rates of capillary stalling in somatosensory cortex that became more pronounced with duration of diabetes. Increased stalling also led to greater pruning of cortical capillaries. Further, the microsphere obstruction assay yielded significantly higher levels of short and long lived capillary obstructions in diabetic mice. Behaviourally, diabetic mice performed poorly in learning/memory tasks as compared to control mice. Conclusions These findings suggests that diabetes is associated with greater risk for capillary obstructions in the brain as well as learning/memory deficits. Our future goal is to explore the underlying mechanisms of increased susceptibility of capillary obstructions and cognitive decline in diabetes condition.

P1-F-144: *Impaired development of social and locomotor behaviours in zebrafish exposed to glyphosate during primary neurogenesis*

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Chemical exposure during prenatal brain development is thought to contribute to the etiology of neurodevelopmental disorders. Glyphosate is the active ingredient in commercial herbicides such as RoundUp? and is the most widely used chemical in agriculture. Exposure to glyphosate prenatally is proposed to cause significant changes to developing brains; however, its exact effects have yet to be elucidated. Here, we hypothesize that environmentally relevant concentrations of glyphosate cause neural changes that lead to alterations in social and locomotive behaviours in larval and adult zebrafish. Embryonic zebrafish were exposed to glyphosate (0.001, 0.1, 10 and 1000 µg/L) from 10 to 48 hours post-fertilization (hpf), a time point that encompasses primary neurogenesis. We found that exposure to environmentally relevant concentrations of glyphosate during zebrafish neurogenesis caused hypoactive swimming upon low-dose exposure (0.001 µg/L) and hyperactive swimming upon high-dose exposure (10 µg/L) in 5 dpf zebrafish. In 10 dpf fish, we observed glyphosate-exposed fish were more hyperactive than their wild-type siblings at all tested concentrations. We also observed changes in locomotion in zebrafish exposed to glyphosate embryonically when startled by a sudden change in light intensity, as a measure of anxious phenotypes. Startle assay results were recapitulated in adult fish, where zebrafish exposed embryonically to higher dose of glyphosate (10 µg/L) had a ~2-fold increase in locomotion. Our findings suggest that exposure to environmental concentrations of glyphosate during neurodevelopment alters the developing brain, leading to lasting changes in behaviour.

P1-F-145: *Contributions of claustro-cortical connections in acute and persistent pain*

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Chronic pain affects approximately 1 in 5 Canadians. While the mechanism underlying chronic pain is unknown, alteration of normal pain processing structures could contribute to its development. The claustrum is a small subcortical structure that inhibits pain processing centers within the cortex, where chronic pain has been associated with enhanced firing. Here, we test the hypothesis that acute nociceptive stimuli will activate claustrum projection neurons leading to a net inhibition of activity in the prefrontal cortex. Furthermore, we hypothesize that chronic pain will reduce claustrum firing leading to enhanced cortical activity and pain hypersensitivity. The Complete Freund's Adjuvant model of hind paw inflammatory pain was used. Claustrum neurons were labeled with fluorescent retrograde tracers to aid in identification. Pain behaviours were assessed with repetitive application of a von Frey filaments. Neuronal activity was assessed with immunohistochemical labeling of the early immediate gene c-Fos. Acute nociceptive stimuli drove c-Fos expression in claustral projection neurons, but not inhibitory neurons. Chronic pain increased claustrum c-FOS expression following innocuous mechanical stimulation. C-Fos activity significantly correlated with the degree of pain behaviour exhibited by the animal. These data indicate that acute pain activates cortical projection neurons within the claustrum, and this activity is enhanced in chronic pain. These data provide initial evidence for a correlation in claustrum activity in acute and chronic pain.

P1-F-146: *Dopamine neurons in the nucleus accumbens and ventral tegmental area influence decision making in a mouse delayed discounting T-maze task*

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Delayed discounting (DD) is a phenomenon where individuals devalue a reward associated with a temporal delay. Several lines of evidence indicate that dopaminergic circuits play an important role in DD decision making and impulsivity. However, DD has historically been investigated in rats and we sought to develop a mouse DD T-maze task to further study dopaminergic circuits using genetic tools. Here, we used tyrosine hydroxylase transgenic mice (TH-Cre) to selectively target dopamine (DA) neurons in the nucleus accumbens (NAc) or ventral tegmental area (VTA) with Cre-dependent excitatory and inhibitory DREADDs. Adult male and female TH-Cre mice received 5 days of maze habituation with their cage mate and then underwent an individual training session where they received 5 large rewards (6 sucrose pellets) and 5 small rewards (1 sucrose pellet) at the end of each T-maze arm. Mice then underwent 10 free-choice trials/day until reaching >80% preference for the large reward on two consecutive days. Once mice met training criteria, they underwent 6 days of DD

where choosing the large reward incurred a 10s delay. The DREADD agonist C21 was injected 1 hr prior to behavioural testing on DD days 5 & 6. Overall, we found that inhibiting DA neurons in the NAc or VTA decreased preference for the small but immediate reward during DD. Excitatory DREADDs had no effect on small vs large reward decision, but significantly increased the latency to decision. Taken together, these results suggest that DA neurons in the NAc and VTA influence decision making in a mouse DD T-maze task.

P1-F-147: *Alcohol and vapourized nicotine co-exposure during adolescence induces sex-specific behavioural effects in adulthood*

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AIM: Co-occurrence of e-cigarette use and alcohol consumption during adolescence is frequent. However, little is known about their long-lasting effects when combined. This highlights the importance in elucidating the consequences of concurrent alcohol and nicotine vapour exposure during such a vulnerable developmental period. METHODS: Four groups of male and female Sprague Dawley rats (n=8-11/group/sex) received either nicotine (JUUL 5% nicotine) or vehicle vapour (30:70 propylene glycol to glycerol) daily from postnatal day 30-46, while having continuous voluntary access to ethanol (10% v/v) and water during this time in a two-bottle preference design. Upon reaching adulthood, all rats underwent behavioural testing using Pavlovian conditioned approach testing and fear conditioning. RESULTS: Male rats exposed to vapourized nicotine with or without alcohol drinking during adolescence exhibited altered reward-related learning in adulthood, evidenced by enhanced levels of sign-tracking behaviour. Male rats that drank alcohol with or without nicotine vapour in adolescence showed deficits in associative fear learning and memory as adults. In contrast, these effects were not seen in female rats exposed to alcohol and nicotine vapour during adolescence. CONCLUSION: The present study provides experimental evidence that co-exposure to alcohol and vapourized nicotine during adolescence in male, but not female, rats produces long-term changes on reward-elicited and cognitive-related behaviours. These findings enhance our understanding of the effects of alcohol and nicotine vapour exposure in adolescence and highlights potential sex differences that exist in the response to their use.

P1-F-148: *Effect of testosterone on behavioural flexibility in male rats*

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Behavioural flexibility, a complex executive function, is the ability to alter actions in response to changes in the environment in order to achieve specific goals. Behavioural flexibility is regulated in part by dopamine signaling within the mesocorticolimbic system, including the ventral tegmental area, nucleus accumbens, and medial prefrontal cortex. In addition, we have shown that testosterone is produced locally within the mesocorticolimbic system. In rodents, behavioural flexibility can be measured using a set-shifting paradigm that requires animals to switch from a visual-cue rule to a side rule, or vice versa, for reward. Using this task, we have previously shown that systemic testosterone treatment impairs set shifting, and inhibition of systemic testosterone synthesis via abiraterone acetate (ABI) improves set shifting when shifting from the visual-cue to side rule. In our current study, we investigate the role of neurally-produced testosterone in set-shifting. Adult male Long-Evans rats were gonadectomized to eliminate systemic but not neurally-produced testosterone and subsequently received either ABI or control treatment during set-shift training and testing. Preliminary data show that neurally-produced testosterone alters set-shifting behaviour. Data collection and analysis on their cue-to-side or side-to-cue rule shift performance are still ongoing. These data will provide novel insight on the role of locally-produced testosterone on behavioural flexibility in male rats.

P1-F-149: *The unique effect of MJN110 (MAGL inhibitor) in hyperdopaminergic states: implications for 2-AG modulation in psychosis.*

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Background: The endocannabinoid system (ECS) is dysregulated in schizophrenia (SCZ). 2-arachidonoylglycerol (2-AG), a major endocannabinoid, is primarily metabolized by monoacylglycerol lipase (MAGL). Elevated 2-AG is observed in individuals at high risk of psychosis, along with altered expression of biosynthesis enzymes of 2-AG in SCZ. MAGL inhibitor (MAGLi) clinical trials are currently underway. However, before wide therapeutic use, it's imperative to fully understand the effect of MAGLi in aforementioned psychopathologies. A subpopulation with dysregulated 2-AG may be vulnerable to psychiatric effects of MAGLi. Therefore, to address 2-AG modulation in SCZ, we assessed pre-clinical effects of MAGLi in models of hyperdopaminergia, as it's well established that SCZ is strongly associated with increased subcortical dopamine. Results: DATKO mice present with subcortical hyperdopaminergia, exhibiting exploratory hyperactivity, anxiety-related changes, impaired sensorimotor gating, and blunted/absent response to psychostimulants. Acute MJN110 treatment exacerbated hyperlocomotion in DATKO and caused deficit in habituation of the acoustic startle response. Furthermore, MJN110 was rewarding in DATKO, but not WT littermates, suggesting exacerbation of hyperdopaminergic states in presence of MJN110. MJN110 effects weren't limited to

genetic models; MAGLi exacerbated psychostimulant responses in C57Bl/6J. Data show that MJN110 effects in both genetic and pharmacological models of hyperdopaminergia are mediated by CB1. Lipidomic analysis of striatal tissue confirmed the ECS is dysregulated in DATKO. Conclusion: Our data highlights how states of hyperdopaminergia may be highly sensitive to 2-AG modulation by MJN110; 2-AG elevation may further drive psychopathology.

P1-F-150: *Changes in mental health and their impact on cognition during the COVID-19 pandemic in older adults with history of depression, mild cognitive impairment, or normal cognition*

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Older adults may be vulnerable to worsening cognition during pandemics due to public health restrictions that increase social isolation and negatively impact mental health. We assessed mental health outcomes during the COVID-19 pandemic and their relationship with cognitive status at 6-months in older adults with remitted major depressive disorder (rMDD), mild cognitive impairment (MCI), or normal cognition (NC). We recruited 108 participants [37M, mean age=71 (SD=±5.75); 71 NC, 21 rMDD, 16 MCI] who completed self-report measures of depression, anxiety, general stress, post-traumatic stress, and the Clinical Dementia Rating Scale (CDR) at baseline, 3 and 6 months. Repeated measures ANCOVA of mood and cognitive measures with time as a within-subject factor, and covariates of the parent study and mood/memory diagnosis, assessed change over time in mental health and cognition. Regression modelling of CDR Sum of Boxes (CDR-SB) score at 6 months with baseline mood and anxiety scores as predictors plus covariates age, gender, parent study, and mood/memory diagnosis was used to assess the association between mental health and future cognition. Mood and cognition did not vary by time. Depression and general stress predicted CDR-SB, accounting for 14% of its variance (B=.28, p=.038; B=.21, p=.088, respectively). These findings are consistent with epidemiological associations between depression/stress and dementia risk and suggest the need to address adverse mental health outcomes in seniors during the COVID-19 pandemic to potentially reduce risk of future cognitive decline.

P1-F-151: *The impact of an object recognition memory test on the brain vascular system*

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Experiences linked to emotions, positive or negative, impact memory consolidation and its associated brain regions. Posttraumatic stress disorder is an example of very strong negative emotions which affect memory by flashbacks of past traumas. Major depressive disorder is another condition in which stress-related memory deficits are observed. We recently highlighted blood brain barrier (BBB) alterations associated with chronic stress and depression. However, little is known about the link between emotional valence, memory encoding and BBB function. Here, we investigated the effects of neutral emotional valence by using the novel object recognition test (NOR), on memory performance vs BBB integrity in mice. We performed NOR under various experimental conditions (arena size, handling, age) and evaluated behavioral performance of male and female mice using Ethovision software. Our results show that expression of genes related to BBB integrity are altered in line with learning and memory processes in a region-specific manner. We observed correlation s between poor learning, anxiety, stress-related corticosterone release and changes in BBB-related gene expression. Together, these results suggest that NOR testing has an impact on the neurovasculature. Although this is known as a neutral valence test, NOR experimental conditions impact behavioral response, highlighting the importance to minimize anxiety when performing rodent behavior paradigms. Memory experiences with positive and negative emotional valence are ongoing to compare their effects on BBB integrity.

P1-F-152: *A polygenic score of neuronal plasticity moderates the association between cognitive performance and cortical thickness in adolescents*

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Although many studies of the adolescent brain identified positive associations between cognitive performance and cortical thickness, little is known about the underlying mechanisms. With the cerebral cortex being one of the key substrates of experience-induced plasticity, inter-individual variations in its thickness could inform us about the genetic contribution indexed by a polygenic score of neuronal plasticity (PGS-NP). Here we studied associations between PGS-NP, cognition, and thickness in the Saguenay Youth Study (533 females, 496 males; mean age=15.0±1.8 years). Using Gene Ontology, we first identified 199 genes implicated in NP, and marked by 155,600 SNPs. Second, we estimated their effect sizes from an educational attainment meta-GWAS (PMID: 30038396) to build a PGS-NP. Verbal (VIQ) and performance (PIQ) IQ scores were cognitive predictors, and thickness of 34 cortical regions were dependent variables. Sex-specific regressions evaluated main effects of cognitive scores, PGS-NP, and the interaction term for all regions. Males with low (vs high) PGS-NP

showed a weaker association between PIQ (but not VIQ) and cortical thickness (p=3.29e-7); a significant interaction was observed between PGS-NP and PIQ (p=0.002). In females, we observed no differences between the low (vs high) PGS-NP groups for the VIQ/PIQ associations with thickness; a significant crossover interaction was found for VIQ (p=3.75e-06). Results suggest that a genetic predisposition may contribute to the emerging brain signatures of specific cognitive domains during adolescence in a sex-specific manner.

P1-F-153: *Vascular and blood-brain barrier-related changes underlie stress responses and resilience in female mice and depression in human tissue*

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Prevalence, symptoms, and treatment of depression suggest that major depressive disorders (MDD) present sex differences. Social stress-induced neurovascular pathology is associated with depressive symptoms in male mice; however, this association is unclear in females. Here, we report that chronic social and subchronic variable stress promotes blood-brain barrier (BBB) alterations in mood-related brain regions of female mice. Targeted disruption of the BBB in the female prefrontal cortex (PFC) induces anxiety- and depression-like behaviours. By comparing the endothelium cell-specific transcriptomic profiling of the mouse male and female PFC, we identify several pathways and genes involved in maladaptive stress responses and resilience to stress. Furthermore, we confirm that the BBB in the PFC of stressed female mice is leaky. Then, we identify circulating vascular biomarkers of chronic stress, such as soluble E-selectin. Similar changes in circulating soluble E-selectin, BBB gene expression and morphology can be found in blood serum and postmortem brain samples from women diagnosed with MDD. Altogether, we propose that BBB dysfunction plays an important role in modulating stress responses in female mice and possibly MDD.

P1-F-154: *An anomalous pyramidal cell type in the subiculum displays sustained cellular activity and robust responses to novelty*

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Introduction: This research investigates an anomalous excitatory cell type, termed "deep cells", that sit in the deepest layer of the subiculum of the hippocampus. The morphology of deep cells significantly differs from other excitatory cells that occupy the subiculum, and thus is suggestive of a specialized function. This work uses in vivo calcium imaging to identify the function of this unique cell type during behavior. Methods: Our lab has constructed a transgenic cre line to access this deep cell type. We use this mouse line to image deep cells during spatial navigation and novel object recognition tests. During these experiments, I use wire-free 1-photon miniscopes to image the dorsal subiculum while mice undergo novel object location and recognition tests, repeated over several timepoints that span 100 days. Results: Data from this project show that deep cells act on timescales of seconds to minutes, and have robust, sustained activity that respond to encounters with novel, local objects. Deep cells show large increases in activity after interaction with a novel object on day one and this activity is substantially reduced in response to this same object on future days. Intriguingly, this increase in activity is still reduced even 100 days after initial introduction to an object. In comparison to classical excitatory cells that make up much of the subiculum, deep cells show novel object-specific activity and no classic spatial phenotypes expected from excitatory cells in the subiculum. Conclusion: Our work here reveals a seemingly spatially uninvolved, novelty-driven, and morphologically distinct cell type previously undescribed in the subiculum.

P1-F-155: *Claustrum lesions lead to changes in behavioural strategy during reversal learning in a spatial memory task*

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The Claustrum (CLA) is a small subcortical region located between the insula and the putamen. Even though it has been shown that the CLA is directly connected to key structures that regulate memory processing such as prefrontal (PFC), anterior cingulate (ACC), retrosplenial (RSC) and entorinal (MEC) cortex, its potential role in memory-related mechanisms has yet to be explored. Thus, we aim to investigate whether the CLA is involved in memory processes by focusing on spatial memory. To test this, we specifically lesioned CLA cells projecting to PFC, ACC, RSC and MEC via stereotaxic injections an of apoptosis-inducing virus. Two weeks later, lesioned and control mice were placed on a modified Barnes maze. Our 10-day protocol included 4 days of training, 3 days reversal training and ending with a probe trial 24h following the end of each training sessions. Control and lesioned mice exhibited similar behavior and were capable of spatial learning and spatial memory during the training phase and the probe test, respectively. However, during the reversal training phase, lesioned mice favoured spatial strategy, whereas control mice used preferentially serial strategy. Nevertheless, during the reversal probe trial, there was no significant difference in spatial memory between both groups. To

conclude, lesioning the CLA seems to affect behavioural strategy choice while not having a direct impact on spatial memory.

P1-F-156: *A biosignature of social stress in male mice*

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Introduction. In human and animal models, biomarkers associated with stress and depressive-like behavior have been found. However, biological profiles should be defined to better understand the dynamics of these biomarkers related to social stress. Therefore, this project aims to define biosignatures associated with social stress and behavioral phenotypes in male mice living in a naturalized environment. Methods. Ten male mice freely interacted with each other in a vivarium for 10 weeks. Tube test was performed to monitor hierarchy. Blood and feces samples were taken to analyze immune and microbiome profiles. Three time points were established to monitor hierarchy and biological samples. Behavioral tests were performed after the experimental timeline. Chronic social defeat stress (CSDS) was used as a social stress control. Results. After ten weeks stable hierarchical organization was observed. Immune and microbiome profiles varied according to social and emotional status. Immune cell populations were associated with cytokines and specific behavioral outputs which were reproduced by CSDS. Social stress in the vivarium and after CSDS also induced a consistent microbiome reorganization. Conclusion. Our results suggest that social stress induces variations in the proportion of immune cell populations, cytokines and microbiome constitution that associate with social and emotional status in male mice. These biosignatures could serve as biomarkers for preventing and monitoring disease progression and predicting treatment response.

P1-F-157: *Novel Enrichment Paradigm Leads to Long-term Enhancements in Object Discrimination in the Triple Transgenic Alzheimer's Mouse Model: Evidence for the Theory of Cognitive Reserve*

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Cognitive reserve (CR) theory posits that people with enriched lifestyles develop the capacity to maintain cognitive function despite brain damage. The Environmental Enrichment (EE) model has been used to study CR theory in rodents, though drawbacks such as lack of standardization and experimenter control leave more to be understood of the enrichment-induced cognitive benefits. Here, we present a novel enrichment paradigm, the Enrichment Track (ET), a course where obstacles

are swapped, rotated, and added to the track daily. Included in the study is also an Enrichment Housing (EH) group, based on traditional EE protocols; exercise Control Track (CT), a track consisting of plain hurdles; and Standard Housing (SH). Following the 8-week enrichment period after weaning, cognitive ability was compared across groups of male Wildtype (WT) and triple transgenic (3xTg) Alzheimer's Disease (AD) mice on a task of invariant object recognition - an early deficit in AD patients. In this task, mice explore two identical objects. After a delay, the mice are re-presented with the original objects in a choice phase in which one object is rotated 90 degrees. Lack of exploration of the rotated object suggests the mouse recognizes the object despite changes in orientation. Only ET mice were able to recognize the rotated object with 5- and 30-min delays, with 3xTg and WT mice performing comparably. These results persisted at 9 months of age suggesting that early-life enrichment provided by the ET produces robust long-term cognitive enhancements that may reverse visual deficits seen in AD.

P1-F-158: *Effects of an oxytocin receptor antagonist on estrogens' facilitation of social recognition in the medial amygdala of female mice*

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Social recognition (SR) is a critical cognitive skill required for animals' successful participation in its social group. Estrogens (E) and 3 of their receptors, ERa, ERb, and GPER1 have been shown to impact SR performance. E interact with other neurochemicals such as oxytocin (OT). Previous research has shown infusions of a subeffective dose (75nM) of an oxytocin receptor antagonist (OTRA) into the medial amygdala (MeA) prior to an infusion of 17-b estradiol (E2) into the PVN prevents E2 rapid facilitating effects on SR. E2 and agonists for all 3 ERs rapidly facilitate SR when infused directly into the MeA. Whether an E2/OT interaction occurs also within the MeA, is unknown. If an interaction exists, the OTRA will block the facilitating effects of E2 in the MeA, while not blocking natural SR occurrence. 10nM and 25nM doses of E2 were employed, as they both facilitate SR in the MeA. Ovariectomies were conducted to reduce circulating E levels to diestrus, and cannulae were surgically implanted into the MeA. The test mouse was administered 75nM OTRA, or a vehicle of artificial cerebrospinal fluid (aCSF) into the MeA. After 2 minutes the test mice received 25nM/10nM of E2 or aCSF into the MeA. Next, the test mouse underwent a "difficult" SR paradigm. An object recognition (OR) paradigm was employed to determine whether facilitating effects of 25nM E2 in the MeA were social specific. It was predicted infusions of OTRA would prevent facilitative effects of E2 in the SR paradigm but would be social specific. Preliminary results indicate 10nM and 25nM of E2 when paired with aCSF facilitates SR, but when paired with the OTRA does not, supporting our hypothesis that E2 rapid facilitation of SR in MeA requires OTRs. No significant findings were revealed in the OR paradigm.

1G. Novel Methods and Technology Development

P1-G-159: *Repairing embryoid bodies restore the normal development and cytoarchitecture of novel brain organoids with cells of astrocyte, microglia, neuron and oligodendrocyte lineage*

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Brain organoids are three-dimensional cultures of different cell types derived by manipulating differentiation of inducible pluripotent stem cells (iPSCs). These organoids emulate the functions and cytoarchitectural changes associated with the developing human brain and, thus, offer a model to study the effects of exogenous and endogenous exposures on the developing human brain (from fetal to neonatal) without the confound of the parental placental environment. The initial stage of brain organoid growth involves the formation of an embryoid body (EB), which is a sphere of iPSCs. Experimental evidence suggest that inadequately formed EBs arise from substandard iPSCs. Using the same culture source of iPSCs, we demonstrate that inadequate EBs can be repaired within 24 hours post-exposure to a newly formulated in-house medium. Repaired EBs can be differentiated into brain organoids using our protocol. Importantly, these organoids are comprised of astrocytes, neurons, oligodendrocytes, and microglia. The latter cell type is often missing from brain organoid cultures. After 90 days in culture, brain organoids arising from repaired EBs exhibit spatial distribution and expression levels of cell markers similar to brain organoids arising from undamaged EBs. This suggests that repairing EBs has no effect on the fate and function of cell and tissue architecture of brain organoids, thus mitigating any risk of 'wasted' cultures due to disruption of the EB, while achieving the cost efficiency needed to facilitate the wider adoption of this model by researchers.

P1-G-160: *Effects of Different Handling Methods on the Behavior of Adult Zebrafish*

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The zebrafish is a frequently employed research subject in biology studies. With increasingly sophisticated methods, scientists are probing subtle biological changes induced in these teleosts. Most procedures with zebrafish include some form of human handling, which may significantly affect the fish. Furthermore, inter- and intra-individual experimenter variability in handling may reduce replicability and reproducibility of results. Unfortunately, despite the potential importance of human handling, the literature is devoid of systematic analyses of the effects of handling

methods/procedures. In this study, we started to address this hiatus. At age 5 months, we randomly assigned wild-type zebrafish to one of four commonly used handling conditions (net stressor, chasing, beaker, pouring). Subsequently, we monitored the behaviour of the fish in an empty tank for 5 minutes and recorded and analyzed their swim paths using Ethovision tracking system. We found significant handling procedure dependent behavioral effects. For example, pouring fish from its home tank to the testing tank without direct net handling reduced total time spent immobile, increased total distance travelled, and increased immobility frequency, suggesting lower anxiety levels and increased exploratory activity. Conversely, in response to netting and chasing procedures, we found zebrafish to exhibit elevated immobility duration, reduced distance swam, and increased intra-individual temporal variance of turn angle. Our results demonstrate the importance of establishing a correct handling procedure in zebrafish studies and imply the need to standardize handling procedures within and between studies to enhance reproducibility and replicability of results.

P1-G-161: *Investigation of transcranial ultrasound-induced neuroplasticity of the human motor cortex by magnetoencephalography*

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Low intensity transcranial focused ultrasound stimulation (TUS) is an emerging technology for non-invasive brain stimulation (NIBS) that can be used to target deep brain structures with more focal stimulation compared to currently used forms of NIBS. tbTUS is a promising protocol for NIBS, however, its mechanism of action is unknown. Using transcranial magnetic stimulation (TMS) and magnetoencephalography (MEG), the aim of this study was to elucidate the effects of tbTUS on oscillatory brain responses and network connectivity. 15 right-handed healthy subjects attended three study visits: one for anatomical MRI and two for experiments with real or sham tbTUS interventions in random order. TMS and tbTUS were delivered to the motor representation (hotspot) of the right first dorsal interosseous (FDI) muscle in the left motor cortex. Before and after each tbTUS intervention, recordings of motor-evoked potentials (MEPs), short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF), and MEG recordings of oscillatory brain activity during resting state and index finger abduction-adduction task were made. TMS demonstrates increased MEP amplitude and decreased SICI following tbTUS, with an absence of changes in ICF. MEG spectral power analysis revealed TUS-mediated statistically significant alterations in alpha power within the supplementary motor cortex (R>L) and changes in beta power within the right basal ganglia and parietal regions. Coherence analysis revealed increased local connectivity in motor centers overlapping with those identified on spectral power analysis. The results provide insights into the

neurophysiological basis of TUS-mediated neuroplasticity and altered motor network activity mediating this sustained response.

P1-G-162: *A multiscope for simultaneous multicolor imaging and stimulation in four brain regions of freely behaving animals*

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Advances in technology are opening new windows on the structural connectivity and functional dynamics of brain circuits and their role in health and disease. Optogenetic modulation combined with imaging provides insight into the role of, and dynamic interplay between, neuronal populations in driving specific behaviors. Here we report the development of a novel multiscope that simultaneously and longitudinally images and modulates neuronal activity in up to four areas of the animal brain or spinal cord. Transgenic mice or viral expression is used to express cell-type specific multicolor fluorescence tags, such as GCaMP and RCaMP, and cell specific optogenetics tags, such as Channel Rhodopsin and ChrimsonR. Four highly flexible imaging optical fibers connect to individual chronically implanted graded refractive index (GRIN) lenses. Each imaging optical fiber simultaneously transmits three different illumination colors: blue for GFP imaging or Channel Rhodopsin stimulation, green for RFP imaging and red for red-shifted optical stimulation. Each color is independently controlled as a continuous wave for imaging or as varying duty cycle pulses for optogenetics. Single neurons can be imaged with high resolution and with minimal distortion across the field of view. This multiscope enables an accurate multiregional longitudinal assessment of neuronal subpopulations, in freely behaving subjects. The resulting circuit-level readout of the underlying mechanisms accelerates our understanding of brain function and helps optimizing therapeutics for brain disorders.

P1-G-163: *Mapping inter-individual functional connectivity variability in TMS targets for major depressive disorder*

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Background: Repetitive transcranial magnetic stimulation (rTMS) is an emerging alternative to existing treatments for major depressive disorder (MDD). Previously, rTMS target sites have focused on individual brain regions implicated in MDD, such as the dorsolateral prefrontal cortex (dlPFC) and orbitofrontal cortex (OFC). However, additionally considering the network connectivity of these sites (i.e. wider set of brain regions that are mono- or polysynaptically activated by rTMS stimulation) may

be useful. Objective: Our hypothesis was that individual differences in both E-field variability and functional brain dynamics would lead to significant variability in network engagement. Methods: To determine the E-field, we created a tetrahedral head model from T1-weighted MR images for 121 subjects from the Human Connectome Project (HCP) database. We used the F3 and Fp1 10-20 EEG electrode system to target the left dlPFC and left OFC, respectively. We acquired the resting-state fMRI data for these subjects from the HCP database, to study the functional connectivity of TMS targets. Results: Three major functional networks were targeted across the dlPFC and OFC: the ventral attention, frontoparietal and default-mode networks in the dlPFC, and the frontoparietal and default mode networks in the OFC. Furthermore, the degree to which each network is engaged varied on a subject-by-subject basis, highlighting inter-individual variability of TMS application. Conclusions: Our hope is that these insights prove useful as part of the broader effort by the psychiatry, neurology, and neuroimaging communities to help improve and refine TMS therapy, through a better understanding of the technology and its neurophysiological effects.

P1-G-164: *Investigating Blood-Labyrinth Barrier opening using MRI-guided Focused Ultrasound combined with Microbubbles*

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The inner ear is one of the least accessible organs for therapeutic delivery, due to its location within the dense temporal bone and the presence of the blood-labyrinth barrier (BLB). Low frequency focused ultrasound (FUS) can non-invasively and transiently enhance blood-brain barrier opening for targeted delivery to the brain. Here, we investigated the use of FUS to enhance the permeability of the inner ear's BLB to achieve minimally invasive therapeutic delivery. Male Long Evans rats received unilateral sonication with the administration of microbubbles (MBs) and Gadovist, a gadolinium-based contrast agent; contrast enhanced T1-weighted magnetic resonance (CE-T1w MR) images were used as an early indicator of BLB permeability enhancement. Before and after sonication, auditory function was assessed using auditory brainstem response (ABR) and distortion product otoacoustic emissions (DPOAE) tests. Following FUS+MB exposure, there was a 33% ± 2.3% increase in gadolinium contrast in CE-T1w MR images in the sonicated inner ears relative to contralateral control ears. Furthermore, there were no significant changes in auditory function in the sonicated inner ears relative to the contralateral control ears, measured using ABR and DPOAE tests. This proof-of-principle study shows that FUS+MB exposure can enhance BLB permeability to mediate delivery of large agents to the inner ear. These data support the feasibility of FUS-mediated delivery to treat inner ear disorders; however, further investigation on the safety profile in the inner ear is required for clinical applicability.

P1-G-165: *Novel rotary cell seeding system to produce complex geometry small-caliber tissue-engineered blood vessel model for the study of intracranial aneurysms*

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Intracranial aneurysms (IA) and the subarachnoid hemorrhage that follows have a 50% mortality rate and 30 to 50% risk of neurological morbidity in surviving patients. This neurovascular disease is known for a weakness of the artery wall causing ballooning that mostly occurs in circle of Willis junctions. The objective is to develop a novel rotary cell seeding system to produce a complex junction geometry small-caliber tissue-engineered blood vessel (TEBV) model for the study of IAs. The development of an innovating rotary (360°) system allows uniform cell seeding to produce complex TEBV models. Polyethylene terephthalate glycol (PETG) scaffolds of a "Y" geometry and human cells are placed inside customized seeding chambers. Five seeding chambers fit inside a sphere placed on two motors that allow multiple-axis rotation for 24 hours at 37°C. For proof-of-concept TEBV, human fibroblasts are seeded on the PETG scaffolds then placed in cell culture plates until tissue formation. A highly innovative rotary culture system to produce 3D tissue-engineered microvessels with complex geometry will be presented. Cell seeding and culture parameters (cell density, rotation speed and time) were optimized. TEBV, made from human dermal fibroblasts using the present culture system, will also be shown. This novel rotary system opens the door to the production of TEBV with complex geometry for the study of IAs but also other neurovascular diseases. A greater understanding of IA pathology and early stages of development would allow more accurate evaluation of patient risk, better intervention plans and possibly new treatment development.

P1-G-166: *Study and isolation of corpora amylacea in neurodegenerative disease patients*

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Purpose/objectives: Corpora amylacea (CA) are glycoproteinaceous inclusions particularly accumulating in the brain during the course of normal aging and to a greater extent in some neurodegenerative diseases. Abundant CA are found in a subset of patients with Alzheimer's disease, Parkinson disease, temporal epilepsy and dementia. Although described many years ago, the precise origin and potential function of CA in normal or pathological conditions are still largely unknown. The objective of this study is to perform comparative neuropathological and biochemical investigations on CA formation in Amyotrophic Lateral Sclerosis using post-mortem CNS tissues. Methodology: Post-

mortem brain tissues from end-stage ALS patients were used for colorations and immunocytochemistry analyses. Of particular interest, post-mortem brains tissues were also obtained from patient who requested medical assistance in dying, i.e. at a more early stage od the disease. CAs from these tissues were isolated and lysed for biochemical analyses. Results: We successfully established a protocol to isolate and purify CAs from multiple brain regions. Immunoneuropathological and biochemical examinations will be presented. Conclusion/significance: A greater understanding of CAs will allow us to better highlight the potential function of CA in ALS with an emphasis on the potential role, if any, of these structures may play in the etiology of the disease.

P1-G-167: *MaxLab Live AxonTracking Assay: Label-Free Identification and Functional Characterization of Axons in Neuronal Networks at High-Throughput*

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Axons enable neuronal communication by propagating electrical signals within neuronal networks. Its dysfunction plays a central role in deliberating pathologies such as Parkinson's Disease and Amyotrophic Lateral Sclerosis. Therefore, access to axonal physiology is crucial for studying information processing within neuronal networks and accelerating drug development for neurological disorders. High-density microelectrode array (HD-MEA) technology enables chronic label-free in-vitro extracellular recordings of axonal action potentials in neurons. MaxOne (single-) and MaxTwo (multi-well) HD-MEA Systems (MaxWell Biosystems, Switzerland) simultaneously capture fast propagating action potentials along multiple axons. Here, we present the MaxLab Live AxonTracking Assay, a software which automatically detects and functionally characterizes axonal signals across hundreds of neurons within a network. We reliably identified and measured from axonal arbors in primary neuronal cultures as well as human iPSC-derived glutamatergic and motor neurons over multiple weeks. We tracked the signal propagation to deduce the conduction velocity, axonal length, and number of axonal branches. We found that the neuronal and branch propagation velocity significantly increased between DIV 13 and 20, corresponding to the maturation of the neuronal network. In conclusion, MaxLab Live AxonTracking Assay combined with HD-MEA technology enables reliable access to electrophysiological recordings of axons, providing a novel functional phenotype for neurological disease modelling and drug screening studies.

P1-G-168: *Reliability and consistency of diffuse optical tomography resting-state functional connectivity measurements from the Kernel Flow fNIRS system*

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Though functional magnetic resonance imagining (fMRI) is an established method for studying brain activity, due to high operation cost, limited availability, and restricted set of applicable contexts, its applications are limited. Fortunately, advances in neuroimaging provide a promising alternative to fMRI. Functional diffuse optical tomography (fDOT) is a technique utilizing high-density functional near infrared spectroscopy (fNIRS) to generate tomographic maps of haemodynamic signals which are driven by metabolic activity of neurons. The Kernel Flow (KF) is a new high-density fNIRS system that allows high-quality fDOT reconstructions from a portable and relatively inexpensive device. To assess the capacity of the KF as a research-grade neuroimaging tool, we conducted a multiple test-retest experiment where fNIRS recordings were obtained from 3 subjects across 12 10-minute sessions of eye-open resting state brain activity over several days. Voxel-based Independent Components Analysis (ICA) and parcellation-based functional connectivity network analysis were performed and reliability and consistency were assessed over hours, days, and across subjects. Results showed reasonable reliability within and across subjects, and fDOT was able to recover several fMRI-like features such as modular separation of canonical brain networks and region+network-level anticorrelations. Local and global relationships of fNIRS-based haemodynamic activity to concurrent EEG signals were also assessed. We conclude that the new generation of high-density portable fDOT systems such as the KF have major potential to broaden functional brain measurement in clinics and research. Towards this future, our work comprehensively characterized the quality and consistency of data from these devices.

P1-G-169: *Minimally humanized mouse models for translatable CRISPR gene editing therapy development*

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To develop a new gene therapy, typically the first step is to "cure" a mouse. However, the current collection of mouse models fails to support such therapy development. This is because either the mice are "knock-outs" with no genomic similarity to patients, or they carry a mouse-specific mutation surrounded by mouse DNA. A new genome-based therapy developed with such mice, must bind mouse DNA, and thus is limited to demonstrating proof of principle. In the few mouse strains that carry a human gene, it is often multicopy and results in a phenotype even when not mutant, both situations detrimental to therapy development. Here, we propose a new type of humanized mouse called "CHuMMMs" (CRISPR humanized-minimally mouse models), where the region of humanization is just enough to create a "landing pad" for the genomic therapy. This allows the use of CRISPR HDR technology to make the mice, and it places the humanization and causal mutation in the context of

the endogenous locus, maintaining single copy, normality of expression, and phenotype. We are currently developing CHuMMMs and a genome-editing therapy for the rare blindness, aniridia. Generation and characterization of the humanized non-mutant mouse has confirmed that the minimal humanization (exon 9 of Pax6) alone does not result in a phenotype. We have also generated humanized mouse ESCs carrying the most frequent aniridia patient variant (a SNP in exon 9). These cell lines have already been used to test CRISPR gene-editing strategies. To date, the most successful therapeutic strategy corrected 30% of the variant bases.

P1-G-170: *Firing rate model of basal-ganglia and thalamic nuclei receiving DBS*

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Deep Brain Stimulation (DBS) is an effective treatment for neurological motion disorders; however, the underlying DBS mechanisms remain elusive. To uncover the DBS mechanism, we developed a firing rate model to quantitatively captures the dynamics of the neuronal activity of varying nuclei receiving DBS, including STN, SNr, Vim and Rt--across different DBS frequencies. Our model consists of two blocks: the synaptic function block and the neuronal firing rate block. Using a recent study on the cellular mechanism of DBS, we feed DBS pulses into the Tsodyks & Markram model of synaptic plasticity with biologically-realistic proportions of excitatory and inhibitory synaptic inputs in order to obtain postsynaptic currents. The synaptic function block transfers DBS pulses to the firing rate of neurons through a nonlinear function whose characteristics vary for different substructures. The output of the synaptic function block is considered as the input of the firing rate model expressed by a first order differential equation. The firing rate model governs the instantaneous firing rate of stimulated neurons. To estimate the model parameters, we implemented a machine learning algorithm to minimize the distance from model simulation to the ground truth firing rate obtained from recorded spikes. Our model reproduces the firing rates calculated from both experimental and synthetic data with high accuracy. The estimated model parameters are consistent across different DBS frequencies, justifying the generalizability of our model, and the feasibility of potential clinical applications.

P1-G-171: *A mathematical comparison of intracortical and corticothalamic models of alpha rhythmogenesis*

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Current theories on the generation of alpha (8-12 Hz) rhythmic activity, which dominates EEG signals, emphasize the importance of communication between various cortical and thalamic neural populations. This is represented by two prevailing types of neural population model (NPM), that simulate alpha oscillations as: 1) Recurrent activity and excitatory-inhibitory interactions within cortical column microcircuits; 2) Delayed inhibitory feedback within cortico-thalamocortical loops. Prominent examples of these two cortical and corticothalamic theories are the NPM models of Jansen & Rit (JR) and Robinson et al., respectively. In this study we developed an approach for comparing the dynamical repertoires and parameter space geometries of the JR and Robinson models. The rationale here is that even though these models nominally describe differing neural populations and circuit motifs (e.g. intracortical, corticothalamic), their basic mathematical components, wiring structure, and excitatory/inhibitory sub-motifs can be meaningfully compared. Using this approach, we study their connectivity parameter space, and assess the influence of each loop within the NPM circuit on the stability and frequency of oscillations. We formulate a novel three-dimensional reduction of the five-dimensional coupling strength parameter space of a JR-based model, which allows us to compactly summarize and visualize how the system dynamics change as a function of loop gains. This work contributes to improving our mechanistic and theoretical understanding on candidate theories of alpha rhythmogenesis.

1H. History, Teaching, Public Awareness and Societal Impacts in Neuroscience

P1-H-172: *Adopting arts-based methods to explore sensory disturbances among patients with acquired brain injuries*

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Neurological conditions, whether brain injuries, strokes, or epilepsy, transform us in ways that are hard to explain. They often result in sensorial sensitivities that shape everyday lives in profound ways. Such sensitivities can make certain spaces difficult to work and live in. Fluorescent lights, booming lecture halls, screen ubiquity, strict and inflexible quotidian schedules, and tightly packed rooms can turn mundane spaces into exhausting and hazardous environments. These experiences are often difficult for patients to convey, leaving them frustrated and confused. Scientific models and biomedical practice often dismiss the invisible and felt experiences of patients with neurological conditions - including apathy, exhaustion, synesthesia, sensitivity to noise and light, and transformations of the inner self. Our paper asks -- How might we get at the multisensorial, affective experience of living with neurological conditions? How can we describe that 'otherwise' which is imperceptible and beyond language? Our paper explores the adoption of sensorial and arts-based

methodologies as a means to inquire critically, but creatively, into the experiences of living with neurological conditions. Drawing from a series of interviews with scholars and graduate students who suffer from neurological conditions, we demonstrate the power of arts-based methods to convey the imperceptible. We will showcase a series of artworks (drawings, textile, stained-glass, sound) created and co-created with patients that represent their experience of living with permanent neurological conditions. Our goal is to develop new ways of understanding neurological conditions by concentrating on the embodied and subjective experiences of patients as expressed through creative arts.

P1-H-173: *National Collaboration through the Canadian Open Parkinson Network*

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The Canadian Open Parkinson Network (C-OPN) is a cross-Canada initiative that bridges people, data and resources to accelerate new discoveries in Parkinson's disease (PD) research. C-OPN aims to operate under the principals of Open Science by facilitating rapid sharing of data and samples with Canadian and international investigators. Nine of Canada's top universities and movement disorders research centres from British Columbia, Alberta, Ontario and Quebec are part of C-OPN. The C-OPN database collects de-identified clinical data with comprehensive information about each participant's family history, lifestyle and environment, along with details of their PD symptoms and medications; test results (MoCA, MDS-UPDRS); and a biobank with biomaterials extracted from blood samples (DNA, peripheral blood mononuclear cells and serum). Since its official launch in June 2020, C-OPN has: i) instituted a bilingual REDCap online database; ii) developed a LORIS platform to facilitate an open, user-friendly, data-sharing platform with members; and iii) begun setting-up collaborations and supporting large-scale, high-impact studies. To date, the project has enrolled 845 participants across Canada. By becoming a member of C-OPN, researchers - including principal investigators, graduate students, postdoctoral fellows and personnel - clinicians and industry partners can gain access to this wealth of resources from the Canadian PD cohort. Together, C-OPN seeks to support cutting-edge, multi-disciplinary and multi-site PD-related research studies across Canada and around the world.

Poster Session 2: May 14, 2022

2A. Development

P2-A-1: *Visuospatial attentional detection of oriented Gabor patches in children as a function of birth experience*

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Recent studies have shown that visuospatial attentional performance in 3-month-olds is influenced by their birth experience, that is, whether they were delivered via C-section or vaginally. What is not known, however, is whether birth experience continues to affect attentional performance as children age. Seven- to 8- and 9- to 10-year-old participants' visuospatial attention as a function of their birth mode was tested in a perceptual detection task in which they needed to indicate whether a tilted Gabor patch had been presented. Prior to presentation of the target Gabor patch, either a cue or no cue was briefly presented at the patch location to assess the impact of attention due to birth mode. Results indicated that the 7- to 8-year-olds, delivered by C-section, exhibited lower accuracy in both cue and no cue conditions relative to those delivered vaginally and to all 9- to 10-year-olds. Reaction time differences (no cue mean RT - cue mean RT per participant) were calculated to standardize the measure across participants. Seven- to 8-year-olds delivered via C-section had greater reaction time differences than those delivered vaginally, and the 9- to 10-year-olds delivered via C-section. These findings suggest that C-section birth impacts younger children's attention, perhaps via a speed-accuracy tradeoff and that this impact might wane as they get older.

P2-A-2: *Phonemic discrimination and eye movements in infants*

Shir Bach-Kay[1], Chandan Narayan[1], Scott Adler[1]

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The ability to discriminate between different phonemes is a crucial part of language development in the first year of life. While language acquisition is a sensitive process that shows narrowing of which phonemes are discriminated in infancy, the paradigms that have been used to study this process have a number of shortcomings. To overcome these shortcomings, the present study examined 6-month-old infants' ability to discriminate between two different phonemes by means of an eye-tracking task, the Visual Expectation Cueing Paradigm (VExCP). In this paradigm, one randomly presented phoneme (paired with a central visual stimulus) predicted a visual target on the right side of a monitor screen

and the other randomly presented phoneme predicted a visual target on the left side of the screen. If the infants could discriminate between the different phonemes, then they would correctly make anticipatory eye movements to the target location at a rate greater than chance. Results indicated that 6-month-old infants successfully discriminated between the two different phonemes forming an expectation for the phoneme-target location relations and thereby making correct anticipatory eye-movements to the correct target location at a rate greater than chance. The findings indicate that the VExCP is a valid paradigm by which to study phonemic discrimination and its development in infancy while overcoming the weaknesses of previously used paradigms.

P2-A-3: *Characterizing the impact of delta-9-tetrahydrocannabinol (THC) on early cortical development with cerebral organoid models from healthy individuals and schizophrenia patients*

Begüm Alural[1], Brianna Ball[1], Joyce Ang[1], Hayley Thorpe[1], Steve Sheridan[2], Roy Perlis[2], Jibran Khokhar[1], Jennifer Geddes-McAlister[1], Jasmin Lalonde[1]

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Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive agent of cannabis. Given accumulating evidence that prenatal cannabis exposure can influence human brain development, an important question concerns the precise impact of THC exposure on the growth of neuronal cells. Here, we used cerebral organoids derived from human iPSC lines in conjunction with proteomics and imaging methods to address this question. Of note, since previous studies established that cannabis-use rates and diagnosis of cannabis use disorder are more frequent in schizophrenia (SCZ) patients than non-patient groups, we also searched for differences specific to this neuropsychiatric disorder. First, we present characterization of the 6 hiPSC lines (3 SCZ patients and 3 control individuals) used in our study, including their culture as cerebral organoids alongside the expression of CB receptors (CB1 and CB2) and other common markers. Second, we report the quantitative proteomic analysis of our 6 hiPSCs lines matured for 125 days as organoids where we identified 37 proteins with significant difference in abundance between control and SCZ specimens or resulting from THC application to the culture media. Finally, we highlight ongoing efforts at understanding the connection between specific proteins that we found to be affected by THC, in particular those that are expressed predominantly in synaptic terminals. Together, our work provides tantalizing insights about the impact of THC on neuron biology during prenatal stages of cerebral cortex development, as well as possible connections to psychosis.

P2-A-4: *Longitudinal imaging reveals brain region-specific angiogenesis in the adult mouse cortex using two-photon in vivo imaging*

Alejandra Raudales[1], Ben Schager[1], Craig Brown[1]

[1]University of Victoria

The extent to which capillaries are capable of sprouting new connections in the healthy and fully mature brain remains controversial. Although histological studies have provided indirect evidence of angiogenesis based on single time points, several in vivo time lapse imaging studies have found little, if any evidence of angiogenesis below the pial surface. Recently, we discovered that certain brain regions are resistant to vessel loss with aging, thus opening the possibility that angiogenesis may compensate, in a region-specific manner, to prevent vessel loss. Here we used in vivo time lapse imaging to survey vascular networks in multiple brain regions over several weeks time in adult female and male mice. Our results show that angiogenesis in medial/anterior cortical regions including retrosplenial and sensori-motor cortex is exceedingly rare, consistent with previous findings. By contrast, the number of sprouting capillaries is strikingly elevated in a graded manner towards posterior/lateral regions such as whisker somatosensory and visual cortex, primarily within the first 200µm of cortical depth. We did not observe any sex differences or regional patterns of vessel pruning. Currently, we are probing the molecular mechanisms underlying these differences using AAV mediated endothelial specific knockdown to investigate the effect of vascular endothelial growth factor receptor-2 (VEGFR2) and Notch1 deletion. Our study is the first to describe long-term, brain region specific patterns of angiogenesis under physiological conditions in healthy adult brains in vivo.

P2-A-5: *Integration and decoding of niche signals by adult neural stem cells*

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The adult brain has a remarkable capacity to produce new cells that migrate and integrate into pre-existing neuronal circuits throughout the lifespan of animals. The largest population of adult neural stem cells (NSCs) is located in the subventricular zone (SVZ). They are largely quiescent and their activation is modulated by a number of SVZ niche factors. Calcium (Ca2+) is known to integrate such signals resulting in distinct Ca2+ frequency and amplitude in the cell body of activated and quiescent NSCs. However, NSCs contact most of niche elements via their processes where most of the Ca2+ events occur. The role of Ca2+ activity in NSC processes is unknown. By combining sparse NSCs labeling approach, 2photon ex-vivo Ca2+ imaging and post-hoc immunolabeling for multiple niche elements, we characterized the spatiotemporal dynamics of Ca2+ signals in NSCs processes with event-based analysis tool (AQuA). We found heterogeneous Ca2+ activity patterns in NSCs processes and specialized high activity "hot-spots" where Ca2+ events repeatably occurs. To determine close to which cellular element in the SVZ niche these Ca2+ hot-spots occur, we performed multiple rounds of post-hoc immunolabeling to depict localization of blood vessels, EGFR+ or Ki67+ progenitors,

neuroblasts, GFAP+ cells and microglia. By using spatial statistics, we showed that NSCs display Ca2+ signals near proliferating progeny, and that around 40% of hot spots occurred near EGFR+ cells. Altogether, our data suggest that NSCs exhibit heterogeneous Ca2+ events with spatial clustering into hot-spots and one of the major sources of these events are proliferating progenitors. This suggests for a possible feedback mechanisms from dividing progenitors to NSCs to regulate their quiescence and activation.

P2-A-6: *Endocannabinoid signaling from hypothalamic neurons enhances subventricular zone neural stem cell differentiation*

Edward Sun[1], Jing Wang[1]

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Adult neurogenesis in the subventricular zone (SVZ) is a complex process regulated by many extrinsic and intrinsic factors. We previously reported that cell-intrinsic and cell-extrinsic activity of the endocannabinoid attenuation enzyme, Monoacylglycerol lipase (Mgll), is a key modulator for SVZ neural stem and progenitor cell (NPC) function in vitro. However, it remains unknown the origin of Mgll-modulated signaling in the SVZ niches that regulate NPC function. We recently used both retrograde and anterograde tracing experiments to demonstrate that Mgll-enriched hypothalamic arcuate nucleus (ARC) sends long range axon terminals to innervate into ventral domain of SVZ. From this, we hypothesize that removal of Mgll from ARC impacts ventral SVZ NPC function. To test this, we generated an ARC neuron-specific Mgll knockout model using intracranial injections of AAV-Cre into the ARC of Mgll-flxed mice. We found that depletion of Mgll in ARC neurons accelerated SVZ NPC neuronal differentiation at the expense of depleting the proliferating NPC pool. Intriguingly, we also discovered that Mgll ablation in ARC neurons can increase the astrocyte population, associated with a depleted quiescent neural stem cell pool in the SVZ. This suggests that Mgll removal can enhance a potential conversion of neural stem cells to astrocytes. Furthermore, we report similar observations in a germline Mgll knockout model, suggesting that neuronal Mgll dominates Mgll-mediated signaling in the SVZ. Taken together, these findings provide a holistic understanding of how Mgll regulates neurogenesis in vivo.

P2-A-7: *Deciphering heterogeneous populations of migrating cells based on the computational assessment of their dynamic properties*

Aymeric Ferreira[1], Cédric Bressan[1], Simon Hardy[1], Armen Saghatelyan[2]

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Neuronal migration is a highly dynamic process, and multiple metrics related to cell movement can be extracted from time-lapse imaging datasets. However, the heterogeneity of neuroblast populations can rarely be evaluated with only these parameters. We developed an analytical pipeline that reduces the dimensions of the data by using principal component analysis (PCA). To determine the number of subpopulations, we used the elbow criterion method, which we validated with a decision tree algorithm to use k-means, a non-parametric clustering technique. This pipeline makes it possible to subdivide the migrating neuroblasts into different sub-clusters based on their dynamic properties. We performed time-lapse imaging of migrating neuroblasts derived from distinct adult neural stem cell (NSCs) lineages and showed that neuroblasts derived from the same NSC lineage as well as across different lineages are heterogeneous and can be subdivided into different clusters based on their dynamic properties. Interestingly, we also observed overlapping clusters of neuroblasts derived from different NSC lineages. We further showed that genetic perturbations or environmental stimuli affect the migratory properties of neuroblasts in a sub-cluster-specific manner. Our data provide a framework for deciphering the heterogeneous properties of migrating neuroblasts and their regulation by both intrinsic and extrinsic factors.

P2-A-8: *Early life stress modifies the density of perineuronal nets, excitatory and inhibitory cells in the medial prefrontal cortex and basolateral amygdala of juvenile rats*

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Exposure to early life stress (ELS) increases vulnerability to neuropsychiatric disorders partly by disrupting neuronal firing and connectivity in the corticolimbic system. Such altered firing patterns are associated with disrupted formation of perineuronal nets (PNNs), known to strengthen synaptic inputs by encapsulating various neuron types. Here, we tested whether ELS modifies the ratio of PNN around inhibitory and excitatory cells in the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) of juvenile (P28) rats. We used the limited bedding (LB) paradigm between P1-10 to induce ELS in male and female offspring and brain tissue were processed on P28 for fluorescent RNA in-situ hybridization and immunohistochemical detection to identify VGAT, VGLUT1 and PNN. We found that animals displayed both regional and sex differences as a result of LB, where the BLA was more affected than the mPFC and males were more affected than females. Males exhibited an increase in the density of VGLUT1 cells surrounded by PNN in the infralimbic mPFC, whereas females were unaffected in the mPFC and did not exhibit changes in PNN density. In the BLA, ELS increased VGAT cell density in both sexes, resulting in a lower percentage of VGAT cells colocalizing PNNs. In addition, LB females showed decreased VGLUT1 cell density, which suggests an excitatory-inhibitory imbalance that may contribute to aberrant neuronal activity. A higher number of "labile" VGAT cells in the BLA

might thus represent a functional "marker" of early life stress in young animals. (Funded by CIHR#162376 to CDW)

P2-A-9: *Re-examining adult hippocampal neurogenesis in humans*

Sophie Simard[1], Corina Nagy[2], Maria Antonietta Davoli[3], Zhipeng Niu[2], Jean-François Théroux[4], Naguib Mechawar[5]

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BACKGROUND AND AIM: Neurogenesis is a phenomenon where new neurons are generated from neural precursor cells. The existence of neurogenesis in the adult human hippocampus was first suggested approximately twenty years ago. In recent years, however, the existence of adult hippocampal neurogenesis (AHN) in humans has been widely debated. Here, using novel approaches, we aim to determine whether AHN does indeed occur in humans. METHODS: We used the 10X Genomics Visium Spatial Gene Expression technology on sections from frozen hippocampal samples (Douglas-Bell Canada Brain Bank) from young and middle-aged male adults. To identify the specific cell-types involved in neurogenesis in the subgranular zone (SGZ) of the dentate gyrus (DG), we also performed RNAscope (Advanced Cell Diagnostics) on sections from frozen-fixed DG samples from middle-aged male adults with probes directed against neurogenic markers. RESULTS: Our preliminary results from the Visium platform show expression of different neurogenic markers, including DCX and NCAM1, proxy markers of immature granule neurons, in spots contained in the cluster corresponding to the SGZ. With RNAscope, we identified DCX and NCAM1 expression in the SGZ in both SLC17A7+ cells and GAD1+ cells, suggesting that DCX and NCAM1 expression in this region may not be specific to immature granule cells. CONCLUSION: These preliminary findings are in agreement with the recent literature suggesting that DCX and NCAM1, although present in the SGZ, are potentially insufficient to define immature granule neurons in the adult human DG.

P2-A-10: *Altered purinergic signalling at key developmental timepoints in the Fmr1 knockout mouse model*

Matthew Napier[1], Angela Scott[1]

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Fragile-X Syndrome (FXS), the leading genetic cause of intellectual disability, is a neurological enigma. Arising from the epigenetic silencing of the Fmr1 gene, the absence of the associated mRNA-binding

protein FMRP almost exclusively impacts neurodevelopment. While many researchers have examined how FXS affects neuron pathology, our lab has zeroed in on glial pathology. Astrocytes have been shown to be a driving force behind neurodevelopment issues in FXS via aberrant purinergic signalling, but this pathway has yet to be considered in hippocampal development. To examine this, I began characterizing the purinergic signalling pathway in the Fmr1-knockout mouse hippocampus over a developmental time course. First, using whole tissue protein assays, I discovered that the purinergic receptor P2Y2R was overexpressed at P21, the time of peak hippocampal synapse formation in mice. Interestingly, I also found that the expression of active P2X7 receptors was lower at both P14, a time of high neurogenesis, and P21. After the broad protein level characterization, I began characterizing receptor location to isolate functions that may be compromised. To date, I have found that P2Y2R colocalizes with astrocytes near the DG-CA3 synapse at P21, suggesting P2Y2R may be involved with astrocyte-mediated synapse formation. I have also found that P2X7R colocalizes with early progenitor cells expressing MASH1 at P14, primarily in the migratory stream of progenitors that populates the DG and CA3 regions. These results present promising evidence that purinergic signalling abnormalities in FXS may impact both neurogenesis and synaptogenesis in the developing hippocampus.

P2-A-11: *Redistribution of synaptic inputs in the neonatal rodent auditory brainstem occurs in the absence of acoustically driven activity*

Ziqi (Hugo) Wang[1], Deda Gillespie[1]

[1]McMaster University

Despite the critical role of activity-dependent refinement in optimizing many neural circuits, little is known about the mechanisms underlying inhibitory circuit refinement, or more particularly about how immature cells coordinately refine their excitatory and inhibitory inputs. The lateral superior olive (LSO) of auditory brainstem is a model system for these questions, as the computation performed by the LSO requires that excitatory and inhibitory inputs to individual neurons be not merely balanced, but also precisely co-registered for stimulus frequency. In a neighbouring brainstem nucleus, the developmental redistribution of inhibitory synapses toward the soma is understood to be directed by acoustic activity. We tested whether this holds true in the LSO by collecting tissue from pre-hearing (before postnatal day 12) rats in which we labeled single cells, immunostained for gephyrin and VGLUT1, and reconstructed confocal image stacks of individual neurons with their excitatory and inhibitory inputs. At early ages, excitatory synapses outnumbered inhibitory synapses at the soma. In the week before hearing onset, distributions of excitatory and inhibitory synapses shifted in complementary directions, such that by hearing onset inhibitory synapses outnumbered excitatory synapses at the soma. Synapse redistribution could not be attributed solely to elimination of synapses

or to concurrent changes in LSO cell morphology. In summary, substantial subcellular redistribution of excitatory and inhibitory synapses in the LSO circuit occurs in the absence of acoustic activity.

P2-A-12: *Immature GABAergic Purkinje cells release glutamate onto cells of the cerebellar nuclei*

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[1]McMaster University, [2]McMaster, [3]Northwestern University

Glycinergic projection neurons of the rodent auditory brainstem transiently release glycine, GABA, and glutamate in early postnatal life. Glutamate release occurs during a period of inhibitory circuit refinement and is enabled by the vesicular glutamate transporter 3 (VGLUT3), which has a striking spatiotemporal expression pattern that is closely mirrored in the immature brainstem by that of Synaptotagmin 1. Consistent with the model that developmental refinement of this inhibitory circuit requires glutamate release, loss of VGLUT3 perturbs circuit refinement. To determine whether the glutamatergic transmission observed at immature inhibitory terminals of the brainstem reflects a more general phenomenon, we examined the GABAergic corticonuclear projection of the neonatal cerebellum. To test for markers associated with transient glutamate release in the brainstem, we immunostained tissue from rats and mice postnatal day (P) 1-19. Expression of both VGLUT3 and Synaptotagmin 1 peaked in early life in the cerebellar nuclei, falling substantially by P19. To test for glutamate release from immature Purkinje cells, we made whole cell recordings from cerebellar nuclear cells in slices from P4-6 transgenic (vGAT-cre::ChR2-eYFP) mice. Optogenetic stimulation of GABAergic inputs in the presence of GABAzine revealed excitatory synaptic currents (50-500 pA) that were blocked by antagonists of AMPA and NMDA receptors. These data illustrate a presynaptic mechanism, in addition to control of postsynaptic chloride, by which immature inhibitory synapses can generate depolarizing responses.

P2-A-13: *Genomic characteristics of Rett syndrome modifier genes*

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Genetic modifiers are non-primary disease-causing genes that alter the severity of genetic diseases. Genetic modifiers have been implicated in neurological disease and may act as therapeutic targets. Rett syndrome (RTT) is a rare neurodevelopmental disorder typically caused by mutations in the X-linked MECP2 gene. While skewed X inactivation has been implicated in the variable severity of RTT, genetic modifiers may also play a role. Recently, a large RTT modifier screen in Mecp2/Y mice assessed phenotype improvement following mutagenesis. This study identified 31 genes that improved the RTT

phenotype. To determine which of these genes are most tractable as drug targets, the human phenotypes associated with these 31 genes were identified via the Open Targets Genetics (OTG) database. This resource aggregates results from unbiased genome-wide association studies (GWAS) and performs machine-learning based fine-mapping of significant association signals using the Locus2Gene (L2G) model. GWAS information was extracted from the OTG v6 database for each of these 31 genes, and the results were filtered for signals most attributable to these genes (i.e. L2G score of 0.5 or greater). Of the genes analyzed, fine-mapped signals were detected for 16 genes, representing a total of 215 human trait associations. For these 16 genes, the average number of associations was 13, ranging from one to 69. Over one-third of the trait associations were found in APOA5, which is involved in lipid metabolism. Further, relevant traits included cognitive performance, educational attainment, and cortical surface area. This work will help prioritize the genetic modifiers for further functional genomics work to confirm modifier effects and determine the underlying biological mechanisms.

P2-A-14: *Investigating microglial influences on the function and formation of the postnatal hypothalamic ventricular niche*

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Compared to the neurogenic niches of the lateral ventricles and the hippocampus, much less is known about the hypothalamic neural stem cell (NSC) niche. In general, hypothalamic neural stem potential is thought to reside in tanycytes, which line the third ventricle (3V), although there may also be contributions from nearby parenchymal cells. Intriguingly, recent work in our lab has identified a subpopulation of microglia that lie adjacent to and influence the behaviours of NSCs along the embryonic 3V, raising the possibility that similar interactions persist postnatally and might regulate the development and/or function of the postnatal hypothalamic NSC niche. Here, we asked whether microglia influence the neural stem potential and cellular composition of the postnatal hypothalamic ventricular zone. To start, we used the neurosphere assay to examine the NSC properties of cells surrounding the mouse hypothalamic 3V at postnatal day (P) 2 and P14. Depletion of microglia using the Csf1r inhibitor PLX5622 increased the sphere-forming capacity at both timepoints, but had minimal effects on differentiation capacity. In addition, potential alterations in the integrity of the 3V wall were observed in the P2 PLX5622-treated hypothalamus. These preliminary data suggested that microglia may play a subtle but underappreciated role in regulating the proliferation and self-renewal of postnatal hypothalamic NSCs, and ongoing assessment of ventricular zone cell type-specific marker expression will reveal if microglia also regulate the terminal fate specification of cells within the niche.

P2-A-15: *Determining the effects of early life seizures on hippocampal CA2 pyramidal neurons*

Jeff Correa[1], Aycheh Al-Chami[1], Chris Correa[1], Hongyu Sun[1]

[1]Carleton University

Neurons in the immature brain are hyperexcitable due to their elevated ratio of excitation to inhibition, which can lead to excessive excitability and vulnerability to seizures. Early life seizures (ELS) pose a significant threat to developing neurons and often result in later-life epilepsy and cognitive deficits. Sitting between CA3 and CA1, hippocampal CA2 has recently emerged as a critical region in processing hippocampal-dependent memory, including social recognition memory. Mature hippocampal CA2 has been shown to be more resistant to temporal lobe epilepsy-induced pyramidal neuron loss seen in CA1 and CA3. However, little is known about the effects of ELS on CA2 pyramidal neurons in the developing hippocampus. Here, we hypothesize that ELS can regulate the excitability of immature CA2 pyramidal neurons during the critical period of development. ELS was induced by pentylenetetrazol (50mg/kg, i.p.) in P10 mouse pups. We found that ELS significantly increased the frequency of AMPA receptor mediated sEPSCs, but not sEPSC amplitude in CA2 pyramidal neurons in hippocampal slices from one-hour post-ELS mice, through increasing the probability of neurotransmitter release as evidenced by increased paired pulse ratio of evoked AMPAR EPSCs. These data strongly support an ELS-induced dysregulation of hippocampal CA2 pyramidal neurons in the developing hippocampus. Identifying the potential effects of ELS on the function of CA2 neurons could help determine a novel target for intervention while reversing the long-term effects of ELS.

P2-A-16: *Impaired maternal care causes long term deficits in spatial memory and social recognition in sex-dependant manner in mice*

Aycheh Al-Chami[1], Jeff Correa[1], Teresa Maletta[1], Hanna Issaqzai[1], Hongyu Sun[1]

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Early life stress (ELS) is known to adversely affect a range of cognitive functions including learning and memory to sociability, anxiety, depression, and aggression. However, the type of early life stress implemented appears to play a determining role in mediating the long-term cognitive impairments manifested in adulthood. Whereas a majority of ELS models rely on separating the pups from the dam for a period of time, the limited bedding and nesting (LBN) model mimics the human condition of child neglect, where the dam is stressed and thus exhibits unpredictable behaviors and fragmented maternal care, producing an environment of chronic stress for the pups. With such a complex dam-pup interaction and knowledge that maternal care is pivotal for the sociability of the developing animal, it is unknown whether social recognition is altered after LBN-induced ELS as other hippocampus-dependent cognitive functions are following ELS. Here, ELS was induced by the limited-

bedding and nesting procedure in P2-9 mice. We found that ELS induced hippocampus-dependent learning and memory deficits in male mice and not their counterpart females at P60-70 compared to controls. Importantly, we revealed that p60-70 mice show social recognition deficits in a sex dependant manner subsequent to LBN. These results indicate the vulnerability of the male brain to ELS induced by variation in maternal care, which may allude to a sex-specific differential in the critical period of hippocampal development.

P2-A-17: *The role of ependymal cells cilia beating on the function of neural stem cells in the adult brain*

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Ependymal cells (EC) are multiciliated cells lining the border of the lateral ventricles. These cells are commonly organized in pinwheel structure surrounding the apical endings of adult neural stem cells (NSC) of the subventricular zone (SVZ). EC respond to multiple signalling molecules and beating of their cilia promotes circulation of cerebrospinal fluid. The beating of cilia also creates mechanical forces that may affect the dynamic and function of NSCs. We developed and characterized a new tool allowing to manipulate the beating rate of EC cilia. By using magnetic beads coupled to antibodies against CD-24, a protein presents the surface of EC cilia, we were able to modulate the beating of cilia by applying magnetic field. We validated this tool ex-vivo by showing that binding of beads to cilia does not affect the beating frequency and that exposure to 28 Gauss magnetic field blocks the cilia beating. We next injected beads into the lateral ventricles of adult mice and allowed them to explore freely for 3h the custom-made cages, consisting of two cages connected with a tunnel. Every time when mice cross the tunnel, they are exposed to magnetic field. Few exposures of the mouse injected with CD24-coupled magnetic beads to the magnetic field stopped the cilia movement and increased by two folds the percentage of active NSC (aNSC). To provide mechanistic insights into cilia-beating mediated effect on NSCs, we explored the role of Ca2 -permeable mechanosensitive receptor TRPM3, which is enriched in quiescent NSC (qNSC) as compared to aNSC. Genetic impairment of TRPMP3 expression, by CRISPR-Cas9, increased NSC activation. Altogether our data suggest that EC cilia beating modulates NSCs activation via mechanical forces.

P2-A-18: *The Histone Chaperone Anp32e Regulates Memory Formation, Transcription, and Dendritic Morphology by Regulating steady-state H2A.Z Binding in neurons*

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Rapid removal of histone H2A.Z from neuronal chromatin is a key step in learning-induced gene expression and memory formation, but mechanisms underlying learning-induced H2A.Z removal are unclear. Anp32e was recently identified as an H2A.Z-specific histone chaperone that removes H2A.Z from nucleosomes in dividing cells, but its role in non-dividing neurons is unclear. Moreover, prior studies investigated Anp32e function under steady-state rather than stimulus-induced conditions. Here, we show that Anp32e regulates H2A.Z binding in neurons under steady-state conditions, with lesser impact on stimulus-induced H2A.Z removal. Functionally, Anp32e depletion leads to H2A.Z-dependent impairment in transcription and dendritic arborization in cultured hippocampal neurons, as well as impaired recall of contextual fear memory and transcriptional regulation. Together, these data indicate that Anp32e regulates behavioral and morphological outcomes by preventing H2A.Z accumulation in chromatin rather than by regulating activity-mediated H2A.Z dynamics.

P2-A-19: *Age-dependent maturation of layer 2/3 and layer 5 pyramidal cells of the mouse dorsal peduncular cortex*

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The dorsal peduncular cortex (DP), located at the ventral limit of the ventromedial prefrontal cortex, plays a key role in driving psychological stress responses, through its interaction with the mediodorsal hypothalamus. The proper development of medial prefrontal cortex (mPFC) circuits is thought to influence mPFC-related behaviours through adulthood. In addition, deficits in synapse development or neuronal activity early in life have been linked to neurodevelopmental disorders. Prelimbic and infralimbic cortical layers possess different types of pyramidal cells (PYR) with similar maturation profiles. Here, we examined the development of intrinsic properties and synaptic inputs of DP PYR cells in both layer 2/3 (L2/3) and layer 5 (L5) of C57BL/6J mice during the first postnatal month using whole-cell patch-clamp recordings. We showed a hyperpolarization of the resting membrane potential, a decrease in input resistance and membrane time constant during the second postnatal week in both layers. Action potentials (AP) became bigger and narrower during the same period in L2/3 and L5. In addition, an increase in rheobase, a decrease in after-hyperpolarization amplitude and hyperpolarization of AP threshold occurred during the second week. At the synaptic level, synaptic excitation onto L2/3 and L5 PYR cells plateaued during the second and third weeks, respectively,

whereas synaptic inhibition showed a gradual increase, plateauing during the fourth postnatal week. Our data show similar maturation of intrinsic and synaptic properties of PYR in both DP layers.

2B. Neural Excitability, Synapses, and Glia: Cellular Mechanisms

P2-B-20: *Disinhibition in the anterior cingulate cortex in a model of chronic pain induced depression*

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Studies have shown the implication of the anterior cingulate cortex (ACC) in two comorbid pathologies: chronic pain and depression. In animal models of chronic pain induced depression (CPID), the neuronal activity within the ACC has been shown to change, but the underlying mechanisms remain unknown. While most studies focused on the glutamatergic cells activity, here we characterized the GABAergic cells activity and the efficacy of inhibition onto glutamatergic cells. To achieve this, we used a mouse model of depression-like behaviour induced by neuropathic pain and viral vector-mediated transduction (mDlx promotor) of the light-sensitive channel Channelrhodopsin 2 in GABAergic cells. We conducted simultaneously single-cell recordings and optogenetic stimulations from identified neurons in the ACC in vivo in anaesthetised animals using a micro-optrode we previously designed (Nat Methods 2011). We activated inhibitory neurons by light stimulations at different frequencies to functionally characterize inhibition. We found that GABAergic cells in CPID animals are less active than in control animals. Presumed glutamatergic cells in CPID animals are also less inhibited by light-induced inhibitory drive. This difference in the efficiency of inhibition is consistent with our finding that GABAergic fail to discharge at high frequency upon optogenetic stimulation, plateauing at a three-fold lower frequency than in control animals. Thus, in the CPID model, abnormal activity in the ACC appear to involve impaired inhibition due to a functional dysregulation of local GABAergic neurons.

P2-B-21: *Presynaptic NMDA receptors signal metabotropically in neocortical STDP*

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Recent studies report that NMDARs can signal metabotropically, i.e., without Ca2+ flux. We previously found that, at visual cortex layer-5 (L5) pyramidal cell (PC) connections, presynaptic NMDARs

(preNMDARs) depend on Mg2+ and RIM1αβ to regulate high-frequency evoked release but signal metabotropically via JNK2 to regulate spontaneous release independent of frequency. At L5 PC-PC connections, timing-dependent long-term depression (tLTD) depends on preNMDARs but not on frequency. We therefore tested if preNMDARs signal metabotropically via JNK2 in tLTD. Using quadruple patch, we elicited tLTD at L5 PC-PC synapses in P11-18 acute visual cortex slices by spike-timing-dependent plasticity (STDP). After homozygous RIM1αβ deletion, tLTD was unaffected (deletion 65% ± 7%, n = 10 vs. tLTD 62% ± 4%, n = 15, p = 0.74). The JNK2 inhibitor SP600125, however, abolished tLTD (96% ± 2%, n = 9 vs. tLTD, p < 0.001). Moreover, while postsynaptic dialysis of a JNK2-blocking peptide did not affect tLTD (post peptide 61± 5%, n = 12 vs. tLTD 52% ± 6%, n = 7, p = 0.30), presynaptic dialysis abolished tLTD (pre peptide 96 ± 4%, n = 10 vs. tLTD, p < 0.001), suggesting metabotropic preNMDAR signaling. In agreement blocking NMDAR ionotropic signaling with 7-CK did not abolish tLTD (73% ± 5 %, n = 9, p < 0.001). To summarize, we find that JNK2 mediates metabotropic preNMDAR signaling in neocortical tLTD. These findings show that the textbook view of NMDARs as ionotropic coincidence detectors in synaptic plasticity may need to be reassessed.

P2-B-22: *Multifaceted impact of Ω3-polyunsaturated fatty acids on Kv1.2 channels and inhibitory neurotransmission*

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GABAergic interneurons are known modulators of principal neuron firing patterns and rates. We previously found that Kv1.2 potassium channels are enriched in GABAergic terminals where its downregulation leads to excess GABA release and over-inhibition of Purkinje neurons in Fmr1-KO mice, a Fragile X Syndrome (FXS) model. Docosahexaenoic acid (DHA), a Kv1.2 positive allosteric modulator, normalizes the inhibitory overtone in vitro and rescues behavioral deficits in vivo, suggesting Kv1.2 as a target for FXS. In this study, we created a stable Kv1.2-GFP CHO cell-line and combined electrophysiology and confocal microscopy to investigate the effect of DHA on Kv1.2 activity, expression, and localization. Patch-clamp recordings of these cells revealed that extracellular DHA acutely accelerates Kv1.2 activation and decelerates its deactivation. Using a combination of in silico simulation and site-directed mutagenesis, we showed that DHA produces its allosteric positive effect in channel gating by directly binding to a deep cavity near the voltage sensor (S4) of Kv1.2. Chronically, incubation with DHA increased the Kv1.2 expression at the plasma membrane, suggesting that DHA promotes its translocation from the cytosolic compartments. These mechanistic insights facilitate in silico and high-throughput drug screening and validation of efficacy in cerebellar slices, to search for novel compounds that upregulate Kv1.2 functions as therapeutic candidates to treat FXS and other disorders with loss-of-function mutations in Kv1.2 and over-inhibition. Supported by CIHR, NSERC & CRC(Tier 1)

P2-B-23: *Contributions of local protein synthesis to developmental remodeling synaptic structure and function*

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The heterogeneity of synaptic morphology diversifies the input-output relationships of synaptic transmission and the coding capacity of neural circuits, but little is known about the regulating mechanisms. We employed a combination of immunohistochemistry and in situ hybridization experiments to explore the possible roles of local protein production in regulating synaptic structure and function at the mouse calyx of Held synapse. Using vGlut1 protein as a presynaptic marker, mRNAs encoding cytomatrix protein (septin-5) and calcium channel (Cav2.1), also rRNAs, are found in immature (P7-9) and mature synapses (P18-21). This suggested an intact presynaptic local protein translation machinery. Fewer Cav mRNAs, but not septin-5 mRNAs, were found closer to the release face of mature calyces (within 500 nm) than those of immature ones. In contrast, vGlut1/2 mRNAs were absent in this glutamatergic axon terminal. Interestingly, when the brain slices were briefly exposed to agonists for mGluR1/5 and NMDARs (DHPG and NMDA) to chemically induce long-term synaptic plasticity (Joshi et al, 2007), protein translation (as assayed by puromycylation) was greatly activated in P7-9 postsynaptic neurons. On the contrary, puromycin signal was almost undetectable in the calyces suggesting this induction paradigm selectively activated postsynaptic protein translation. These findings implicated active local protein synthesis in both pre- and/or postsynaptic loci as a potential contributor to the developmental plasticity and morpho-functional heterogeneity of synapses. Supported by NSERC and CIHR

P2-B-24: *Conduction delays in myelinated axons with variable nodal and internodal lengths*

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The generation and propagation of action potentials in white matter are influenced by a fatty substance, called myelin, wrapping around axons. Myelin is formed by glial cells -- oligodendrocytes -- and allows action potentials to transmit faster and without attenuation. An important feature of myelin is its impact on conduction delays, that is, the time it takes for action potentials to reach their destination. Conduction delays play an important role in brain function due to the dependence of neural communication on spike timing. Thus studying conduction delays is of the utmost importance. Previous studies examining action potential propagation along myelinated axons are based on stereotyped cases based on the assumption that myelin sheaths are periodically located along axons

and are thus very symmetric. The question we aim to answer is: do changes in myelin segment distribution, length and thickness, not only along the same axon but also along different axons, influence conduction delays and neural communication across the white matter? We are making a step forward answering this question and estimate conduction delays and the corresponding conduction velocity in the more general case where myelin sheaths of different longitudinal lengths and widths are randomly distributed along single axons. The lengths of nodes of Ranvier, namely the gaps between two consecutive myelin, will also change. How will this impact the propagation of action potentials? What are other parameters affecting conduction delays? We approach the problem using the cable equation and provide both computational and mathematical analysis whenever possible.

P2-B-25: *Ambient glutamate levels regulate unitary quantal properties at a central excitatory synapse*

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Glutamate is the main excitatory neurotransmitter to mediate fast neurotransmission at excitatory synapses and enable communication and computation in the central nervous system. Synaptic vesicles (SVs) are packed with glutamate in the nerve terminal and constitute quantal units that undergo either spontaneous fusion or synchronized release into the synaptic cleft to activate postsynaptic glutamate receptors in the form of miniature (mEPSCs) or evoked excitatory postsynaptic currents (eEPSCs). Contrary to eEPSCs, the key factors that regulate the unitary quantal properties of mEPSCs remain poorly understood. Given that glutamate must be quickly removed from the extracellular space upon unloading from SVs, we explored whether and how ambient glutamate levels regulate quantal properties using the axosomatic calyx of Held synapse as a model system. Surprisingly, we found that increasing ambient glutamate concentration by brief inhibition of glutamate transporters lead to a persistent increase in both frequency and amplitude of mEPSCs, suggesting both presynaptic and postsynaptic mechanisms may underlie changes in quantal properties at central excitatory synapses. We are currently performing experiments to delineate such mechanisms. Our results implicate that unitary quantal properties are highly sensitive to ambient glutamate levels which may potentially be a key determinant of synaptic transmission and plasticity. Supported by NSERC, CIHR, and CRC (Tier 1)

P2-B-26: *A macromolecular protein complex of presynaptic calcium channels for neurotransmission*

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Neuronal communication depends highly on integrating the action potentials with calcium dependent neurotransmitter release through physical couplings between voltage-gated calcium channels (VGCCs) and synaptic vesicles (SVs) at nerve terminals. An evolutionarily conserved set of proteins that form active zones at the synaptic terminals bridges the activity of VGCCs to the fusion of vesicles. Whereas significant progress has been made in uncovering fusion machinery, much remain to be discovered about the release and refilling mechanisms of SVs. In this study, we hypothesize that intracellular domains of P/Q type voltage-gated calcium channels (Cav2.1) may serve as the core scaffold for organizing macro-molecular complex for the release sites. We have developed an experimental approach focusing on Cav2.1 in the cerebellum where this channel is most abundantly found. By combining Mass Spec, FLIM-FRET and super-resolution microscopy and patch-clamp electrophysiology, we identified a series of new interacting proteins with Cav2.1, among which "Protein R" was found dynamically regulate the loading of glutamate into SVs via novel, direct interactions with Cav2.1 and vesicular glutamate transporter (VGLUT), significantly impacting synaptic strength and short-term plasticity. Our long-term goal of this project is to shed light on the modular composition of the active release machinery with "Protein R" as a key building block to better understand the molecular organization of neurotransmission in healthy and diseased brain.

P2-B-27: *Characterizing cerebellar perineuronal nets in humans, mice and macaques*

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Introduction: Perineuronal nets (PNNs) have been shown to restrict neuroplasticity and stabilize synapses. PNNs have been well-characterized in sensory cortices, though little is known about these structures in the cerebellum (CB), especially in humans. This study aims to characterize CB PNNs through a cross-species comparison of mouse, macaque and human brains. Methods: Post-mortem human CB from neurologically- and psychiatrically-healthy individuals were provided by the Douglas-Bell Canada Brain Bank. CB from wild-type mice and cynomolgus macaques were obtained through collaborations. Using immunofluorescence in sagittal and coronal sections, we labelled PNNs using Wisteria Floribunda Lectin (WFL) and anti-aggrecan (ACAN) antibodies. We also labelled parvalbumin(PV)-expressing neurons in animals with an anti-PV antibody. Moreover, fluorescent in situ hybridization (FISH) was employed to label vesicular glutamate transporter 1 (SLC17A7), glutamate decarboxylase 1 (GAD1), and PV to determine the phenotype of cells surrounded by PNNs in the human CB. Results: We observed that across the species studied, WFL+ and ACAN+ PNNs are localized in the CB nuclei. In mouse and macaque we also found WFL+ and ACAN+ PNNs in the CB cortex with differences in expression between markers. FISH experiments revealed that CB PNNs mostly surround PV+ excitatory projection neurons. Conclusion: This work highlights species

differences in the nature and distribution of CB PNNs. As such, it could pave the way for future studies on PNN-related CB neuroplasticity in the healthy and disordered brain.

P2-B-28: *Spatially patterned excitatory neuron subtypes and projections within the claustrum*

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Despite being implicated in consciousness, attention and impulsivity, the structural organization of the claustrum (CLA) remains largely unknown. To better elucidate its breadth of functions, it is crucial that we first understand its intrinsic neural organization. Thus, we sought to investigate the transcriptomic breakdown of the CLA through single-cell RNA-sequencing (scRNA-seq). From our analysis, we uncovered a previously unknown excitatory neuronal subtype, suggesting the CLA is composed of 2 transcriptomically distinct excitatory neurons. To investigate the spatial organization of these subtypes, we used multiplexed fluorescence in situ hybridization (mFISH) on brain sections, targeting RNA from 12 different marker genes chosen from our scRNA-seq dataset. We found that the gene expression patterns of the claustral neurons correlated strongly with our scRNA-seq predictions, organizing into a "core-shell" spatial configuration that was consistent across the anterior-posterior axis. To determine if these transcriptomic signatures corresponded to specific projection neuron populations within the CLA, multicolour retrograde tracing in conjunction with mFISH was performed. Here, we found the core and shell subtypes correlated with distinct projection targets from the retrosplenial cortex and lateral entorhinal cortex, respectively. Thus, the CLA exhibits a "core-shell" spatial organization with distinct molecular and circuit properties, which may drive its functional complexity. This spatial heterogeneity can be used in the future to examine its subtype-specific function.

P2-B-29: *Characterizing astrocytes in the cerebellum: a comparative neuroanatomical study of mice, macaques, and humans.*

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Objective: There is growing appreciation for cortical astrocyte diversity, but less is known in other brain regions such as the cerebellum. We performed a comparative post-mortem neuroanatomical examination of astrocytes in the adult cerebellum of healthy humans, macaques, and mice. Methods: Human cerebella were obtained from the Douglas-Bell Canada Brain Bank. Transgenic mice (ALDH1L1-Cre/ERT2; Rosa26-TdTomato) and cyno macaque cerebella were obtained collaboratively. Sagittal sections were labelled for two canonical astrocyte markers glial fibrillary acidic protein (GFAP) and aldehyde Dehydrogenase-1 Family member L1 (ALDH1L1). Percent area coverages of GFAP immunoreactive (-IR) and ALDH1L1-IR astrocytes were obtained using a threshold approach. Results: Bergmann glia cell bodies were primarily ALDH1L1-IR and localized to the Purkinje cell layer. Their processes were mainly GFAP-IR and spanned the molecular layer displaying increased complexity with species progression. Velate and white matter astrocytes were both GFAP-IR and ALDH1L1-IR with mice exhibiting lower ALDH1L1-IR % area coverage in white matter. In mice, GFAP-IR astrocytes were scarce in the deep cerebellar nuclei. Astrocyte divergence was largest in lobules II, VII, and IX between mice and macaques. Human annotations are ongoing. Conclusions: This study will achieve the first comprehensive characterization of cerebellar astrocytes across species, highlighting glial features unique to humans. It will also guide future studies examining the possible implication of cerebellar astrocytes in brain disorders.

P2-B-30: *High pass filtering properties in the axon ensure high-fidelity signal transmission*

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The role of the axon initial segment (AIS) is to convert graded depolarization (analog) into all-or-none spikes (digital). Axons transmit digital signals to post synaptic neurons. Transduction in the AIS and propagation in the axon are best served by different spike initiation properties (filters). Because of difficulties recording from intact axons, the difference between AIS and axon filter properties is not clear. To study AIS and axon filter properties, we built a multicompartment model of a CA1 pyramidal neuron with a detailed myelinated axon validated by experimental data. Simulations showed that the axon initiates a spike only if its voltage reaches spike threshold before activation of Kv1 channels. Spike triggered average (STA) and spike triggered covariance (STC) analyses revealed that the axon responds preferentially to input with a narrow biphasic waveform, similar to the axial current waveform associated with a spike. In contrast, the AIS exhibited a broad monophasic STA. Spike initiation in the AIS depends only on the amount of depolarization, whereas the axon is also sensitive to the rate of depolarization. In other words, the AIS behaves as a low pass filter (which is well suited for transducing slow, graded depolarization) whereas the axon behaves as a high pass filter (which is well suited for re-initiating spikes during salutatory propagation). By responding exclusively to large,

abrupt inputs, the axon is incapable of generating ectopic spikes in response to graded depolarization or channel noise.

P2-B-31: *Interference of Neuronal TrkB Signaling by Cannabis-Derived Flavonoids*

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Cannflavins A and B are flavonoids synthesized by the Cannabis sativa (C. sativa) plant known to inhibit the biosynthesis of various pro-inflammatory mediators. These molecules are prenylated and highly lipophilic, which allow them to potentially interact with membrane-bound enzymes and receptors. Recent evidence suggests that cannflavins may also have neuroprotective and anti-cancer effects, but the full range of molecular changes induced by these phytochemicals in cells remains to be described. Here, we studied cannflavins in relation to the Tropomyosin receptor kinase B (TrkB), a receptor tyrosine kinase which is activated by the growth factor brain-derived neurotrophic factor (BDNF). Using mouse primary cortical neurons, we first collected evidence that cannflavins A and B prevent the accumulation of the Activity-regulated cytoskeleton-associated (Arc) protein upon TrkB stimulation by exogenous BDNF in these cells. Consistent with this effect, we next show reduced activation of TrkB and downstream signaling effectors mediating Arc mRNA transcription when BDNF is co-applied with cannflavins. Of note, we also performed a screen that demonstrated a lack of agonist action of cannflavins towards G protein-coupled receptors. Finally, we used Neuro2a cells overexpressing TrkB to show that cannflavins can block the growth of neurites and increased survival rate produced by the higher abundance of the receptor in this model. Together, our study offers a new path to understand the reported effects of cannflavins and other closely related compounds in different cellular contexts.

P2-B-32: *Examining the potential influence of perineuronal nets on myelination of axons projected by PV interneurons in the human prefrontal cortex*

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Perineuronal nets (PNNs) are specialized extracellular matrix structures that condense around certain neurons. They are thought to be key regulators of plasticity since their formation has been linked to the closure of critical periods of cerebral plasticity. Recent studies have also highlighted the role

played by myelin in ending critical periods. Neuroimaging studies show that cortical PNNs mostly enwrap at Parvalbumin (PV) interneurons, the axons of which can be myelinated. I hypothesize that PNNs have an influence on PV interneuron myelination in the human ventromedial prefrontal cortex (vmPFC). Postmortem human brain samples offer a unique opportunity to test this hypothesis with multiple-label immunofluorescence and qualitative confocal microscopy. Our preliminary qualitative results indicate that in the human vmPFC, PV neurons can also extend a myelinated axon, as previously described by others in the temporal cortex. We are currently assessing the proportions, layer by layer, of PV interneurons with or without PNNs that are myelinated or not. This research should shed new light on the influence of PNNs on neuroplasticity in the human brain.

P2-B-33: *Maturation of mouse visual cortex astrocytes*

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Mature astrocytes signal via intracellular Ca2+ transients to control plasticity at nearby synapses. We investigated how mouse visual cortex astrocytes mature morphologically and electrophysiologically over postnatal days (P) 3 - 30 and how this relates to changes in spontaneous Ca2+ events. Using 2-photon microscopy (2PM) in acute slices, cortical layer-5 astrocytes were targeted for patching with sulforhodamine 101. Average Vm was -83 ± 0.3 mV and Rinput was 29 ± 1.3 MΩ (n = 196). Across ages P3-30, Vm increased (Pearson's r = 0.438, $p < 0.01$) and Rinput decreased (r = -0.159, $p < 0.05$). Voltage steps in patched L5 astrocytes revealed two response types: a steady, time-invariant conductance, and a slowly activating component. The latter diminished with age (Spearman's rho = -0.44, $p < 0.05$, n = 22). 2PM of Alexa-488 dye loading or biocytin histology revealed that gap-junction coupling increased with age starting around P7 (r = 0.73, $p < 0.05$, n = 24). 3D reconstructions from Alexa 488 loading or biocytin staining revealed increased branch density and reduced extent of branching after P20 based on Sholl analysis. Finally, we visualized spontaneous Ca2+ transients with 2PM of Fluo-5F (200 µM) or AAV-GCaMP6f and found that events decorrelated with age (r = -0.57, $p < 0.01$, n = 20). Ca2+ events also became more frequent (r = 0.581, $p < 0.01$) and shorter with age (r = -0.632, $p < 0.01$). As astrocytes mature, spontaneous Ca2+ activity changes from synchronous cell-wide waves to local transients. This decorrelation may enable localized astrocytic control of synaptic plasticity.

P2-B-34: *Intracellular Ca2+ regulates a lipid-gated TRPC-like cation channel in Aplysia bag cell neurons*

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Non-selective cation currents influence neuronal excitability and are regulated by a variety of factors, such as lipid metabolites and ions. Reproduction in the sea snail, Aplysia californica, involves neuroendocrine bag cell neurons, which secrete hormone during an afterdischarge that is driven in part by a diacylglycerol-gated cation current. We examined the regulatory role of intra- and extracellular Ca2+ as well as the molecular identity of this channel. Whole-cell voltage-clamp recordings were obtained from bag cell neurons in culture for 1-3 days, and cationic current evoked by generating diacylglycerol with the phospholipase C activator, m-3M3FBS. Internal solutions with high (1 µM Ca2+, 5 mM EGTA), medium (300 nM Ca2+, 5 mM EGTA), and low (20 mM EGTA) Ca2+ were used, along with control vs Ca2+-free bath solutions. Current onset following drug bath-application was similar across conditions, at ~2.5 minutes, with a peak of ~-5 nA. Compared to medium intracellular Ca2+, total current area was increased by low, but unchanged by high Ca2+. Removal of extracellular Ca2+ had no effect. The bag cell neuron current resembles certain TRPC channels; we cloned and expressed, in human embryonic kidney cells, an Aplysia TRPC5 channel. Voltage-clamp showed this current to be similar to the native m-3M3FBS-triggered current. Thus, while Ca2+ influx through the channel is likely not a determinant, low intracellular Ca2+, as seen prior to afterdischarge onset, favours channel gating. Overall, an interplay between lipids and Ca2+ may regulate TRPC channels to influence reproduction.

P2-B-35: *Tac1-expressing cells in the pre-Bötzinger complex are potential targets to prevent opioid-induced respiratory depression*

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Rational: Opioids are extensively used for their analgesic properties but they can lead to respiratory depression. The analgesic effect of opioids is due to activation of µ-opioid receptors (MOR) in the central nervous system. Neurons expressing tachykinin precursor 1 peptide (Tac1) located in the pre-Bötzinger complex (preBötC) also co-express neurokinin-1 receptors (NK1R) and MORs. NK1R neurons are preferentially inhibited by opioids and play an essential role in mediating opioid-induced respiratory depression. Objective: Here, we tested the hypothesis that optogenetic activation of Tac1-expressing preBötC cells in freely behaving mice will modulate breathing and prevent respiratory depression by opioids. Methods: Using a Cre-loxP recombination approach, we injected in Tac1 Cre recombinase mice the adeno-associated virus containing the gene cassette of the excitatory channelrhodopsin-2 ChETA flanked between loxP sites. A 200 µm optical fiber was then fixed above the preBötC for laser stimulation with blue light (wavelength: 480 nm). After four weeks, the mouse was placed in a plethysmographic chamber and breathing was measured while laser stimulations (30 Hz) were performed under baseline conditions or following administration of the clinically relevant µ-opioid drug fentanyl (0.3 mg/Kg). Results: Data show that stimulation of Tac1-expressing cells

increased respiratory frequency under baseline conditions. However, stimulation of Tac1 cells did not prevent opioid-induced respiratory depression. Conclusion: Tac1-expressing preBötC cells may constitute a target to modulate breathing but their effect to prevent depression of breathing by opioids seems uncertain. These results will help identify the cells mediating opioid-induced respiratory depression.

P2-B-36: *Vasoactive intestinal peptide-expressing interneurons shape integration of excitatory inputs in hippocampal CA1 pyramidal cells*

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The hippocampal CA1 area vasoactive intestinal peptide-positive (VIP+) interneurons are highly diverse. Two main types are the cholecystokinin-expressing (CCK+) VIP+ cells and the interneuron-selective (IS) VIP+ cells. While CCK+/VIP+ cells inhibit the pyramidal cells (PCs), the IS cells disinhibit the PCs by suppressing particular interneuron types. Whether and how the VIP+ cells modulate PC activity remains elusive. Here, using optogenetic activation of VIP+ cells in the hippocampal CA1 area in vitro, we found that VIP+ cells provide monosynaptic inhibition to both deep and superficial PC subtypes. Next, using chemogenetic silencing of VIP+ cells, we found that integration of both the Schaffer collateral (SC) and the temporoammonic (TA) inputs by PCs was coordinated via VIP+ interneurons. Specifically, disynaptic inhibition was significantly increased following VIP+ cell inactivation, in line with VIP+ cell-mediated disinhibition in the CA1 area. Besides, while silencing VIP+ cells did not affect excitatory postsynaptic responses evoked by SC stimulation, TA EPSPs were significantly increased, revealing additional VIP+ cell-mediated shunting effect on TA input integration. Finally, local field potential recordings in awake mice revealed no changes in theta rhythm parameters upon chemogenetic silencing of VIP+ cells. Together, these data suggest that VIP+ cells in the CA1 area are involved in both inhibitory and disinhibitory circuits and provide a powerful circuit mechanism for coordinating the integration of excitatory inputs and likely specific oscillatory patterns.

P2-B-37: *Modelling effects of deep brain stimulation and plasticity in the basal ganglia*

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Our aim was to model the impact of deep brain stimulation and the importance of the synaptic dynamics and connectivity for effective stimulation. We constructed a network model in Python using NEST consisting of a population of STN and GPe neurons, with connectivity based on anatomical

connectivity ranges found in literature to investigate site specific dynamics like evoked resonant neural activity. Given the importance of high frequency stimulation in deep brain stimulation the synapses were modelled to incorporate short term synaptic plasticity. The results of our model indicate that the dynamics observed when stimulating the STN depend upon the micro-circuitry of the efferent and afferent regions, specifically the degree of recurrent connectivity in the GPe for our model.

P2-B-38: *Axonal protein synthesis regulates synaptic release*

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[1]McGill University

Local protein synthesis (PS) has emerged as a key to localized growth responses in development, by allowing proteins to be synthesized at the right place and time. It has been argued that PS does not occur in CNS axons after synapse formation. Recent imaging and omics studies have nonetheless called this into question, raising the possibility that axonal PS controls neurotransmission. Here, we explored the role of axonal PS in synaptic release from layer-5 pyramidal cells (PCs) in postnatal day 11-16 acute visual cortex slices. PS inhibition by cycloheximide (CHX) wash-in increased spontaneous release rates (140% ± 7%, n = 22, p < 0.001), suggesting that PS controls release probability. Surprisingly, in paired recordings, CHX wash-in instead reduced evoked responses (62% ± 6%, n= 9, p < 0.001). Evoked release was reduced by pre- (47% ± 6%, n = 16, p < 0.001) but not postsynaptic m7G cap analog loading (95% ± 4%, n = 17, p = 0.23), showing that the need for PS was presynaptic. Next, we isolated the axon from the soma by 2-photon laser microsurgery. By direct stimulation of isolated axons, evoked release was stably sustained without presynaptic somatodendrites for >1 hour (100% ± 3%, n = 8, p = 0.18). CHX wash-in, however, reduced evoked release from isolated axons (55% ± 4%, n= 7, p < 0.001), revealing that axonal PS plays a pivotal role in neurotransmission. In conclusion, presynaptic PS differentially controls evoked and spontaneous release, and the site of PS-controlled release is local to the axon.

P2-B-39: *Short-Term Plasticity at Neocortical Vip Interneuron Inputs and Outputs*

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Of all interneuron (IN) types, vasoactive intestinal peptide-expressing (Vip) INs are particularly poorly described, e.g., little is known about their short-term plasticity (STP). We therefore set out to

characterize STP of Vip IN inputs and outputs. We expressed Channelrhodopsin-2 (ChR2) in mouse motor cortex Vip INs by crossing Vip-Cre and Ai32-flox mouse lines. To explore the STP of Vip IN outputs, we patched layer-5 (L5) Martinotti cells (MCs) and basket cells (BCs) in P20-P45 acute slices and activated L2/3 Vip IN inputs using a 445-nm laser. We found that Vip to MC connections short-term depressed (PPR at 30 Hz: 51%±3%, n=53), as did Vip to BC synapses (61%±6%, n=21). To explore input STP, we patched L2/3 Vip INs and stimulated extracellularly, which revealed more facilitation but also a surprising diversity (PPR: 160%±20%, n=31; compared to MC and BC outputs: ANOVA $p<0.001$ and F test $p<0.001$). This PPR diversity did not depend on age ($r=0.166$, $p>0.05$). To explore why input STP was mixed, we tuned a 4-parameter Tsodyks-Markram vesicle depletion model and found a wide range of pr (0.2 to 0.7), whereas facilitation and the two recovery rates distributed tightly. To see if the diversity resulted from recordings from different Vip IN types with distinct input STP, we carried out hierarchical clustering. This, however, indicated a single class of recorded cells. In conclusion, we attributed the heterogeneity of STP at Vip IN inputs to a striking variability in pr. This in turn could be due to individual inputs' history of long-term plasticity, or to different types of inputs.

P2-B-40: *Extended time scale plasticity in the prefrontal cortex provides evidence of eligibility traces permissive to supervised learning*

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Learning is required to optimize behavioural choices. Synaptic plasticity mechanisms, such as Long-term potentiation (LTP), are widely believed to be cellular correlates of learning and memory. LTP can be induced by Spike-Timing-Dependent Plasticity protocols that typically require dozens of near-simultaneous (i.e., tens of milliseconds) firing of pre- and postsynaptic neurons, a timescale fundamentally incompatible with that expected for supervised learning (200ms-2s), and a repetition requirement that is far from that of quasi one-shot learning (1-5x). Eligibility traces, an unknown biochemical process priming synapses to remain eligible for potentiation for an extended period of time (hundreds of milliseconds), have long been hypothesized to provide an appealing solution to this temporal credit assignment problem. However, their existence is unclear. Here, using cellular electrophysiology and 2-photon microscopy, we examined the ability of temporally separated pre- and postsynaptic events to induce potentiation in pyramidal neurons of mice prefrontal cortex. We observed that a few pairings of pre- and postsynaptic events at behaviourally relevant timescale (0.5s-1.5s) reliably and robustly potentiated synaptic strength. This form of plasticity followed unsuspected temporal rules that were dependent on bursting and that were modulated by norepinephrine, a neuromodulator believed to provide saliency signal. We are currently developing a model that captures core aspects of these plasticity rules. The features of these plasticity rules support the

existence of synaptic eligibility traces, and provide a potential avenue of solution to the temporal credit assignment problem.

P2-B-41: *Actin cortex fenestrae in magnocellular neurosecretory cells (MNCs) of the rat supraoptic nucleus (SON)*

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Previous experiments have shown that osmosensory transduction (OT) in rat MNCs is mediated by an N-terminal variant of the transient receptor potential vanilloid 1 (dn-Trpv1) channel. Activation of this channel is mediated by microtubules (MTs) that apply a "push" force to the channel during hypertonicity-induced shrinking. MNCs also feature a thick (~1 µm) layer of actin filaments (f-actin) beneath the plasma membrane, which is also essential for OT, but how f-actin contributes to this process remains unknown. Specifically, it is not known if f-actin interacts with dn-Trpv1 channels and if the actin cortex has specific features that are important for OT. We used immunocytochemistry, proximity ligation assay (PLA) and super-resolution imaging to examine the actin cytoskeleton of isolated MNCs of the rat SON. PLA confirmed previously known MT-Trpv1 channel interactions (Prager-Khoutorsky et al. 2014). Specifically, we observed ~10-100 interaction sites per cell (n=30; 6 preparations), mainly discrete puncta scattered on the cell surface. However, no interaction sites were detected when PLA was performed using antibodies against actin and trpv1 (n=20, 2 preparations). We used super-resolution fluorescence microscopy with a FV 3000 Olympus confocal microscope and image deconvolution (CellSense software, Olympus Canada Ltd) to obtain image stacks of the MNC actin cytoskeleton. These images revealed that the submembrane actin cortex is non-uniform, with small regions (~1-5 µm) of lowered fluorescence (n=50; 2 preparations). To conclude, this study reveals that the submembrane actin cortex of MNCs is fenestrated and does not interact with dn-Trpv1 channels.

P2-B-42: *Astrocyte metabolic networks in sleep-wake behaviours.*

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The metabolic support role of astrocytes has been shown to coordinate many complex behaviours including sleep-wake cycles. Specifically, astrocytes in the lateral hypothalamus modulate the excitability of orexin neurons by dynamically controlling the availability of energy substrates to drive sleep-wake cycles. Despite detailed characterisation of this process, the underlying mechanisms tuning circadian fluctuations in astrocyte metabolic support remains unknown. Considering overwhelming evidence of sleep-wake perturbations in stress related psychiatric disorders, we hypothesize that astrocyte metabolic support of neuronal activity is dynamically regulated by circadian fluctuations in blood glucocorticoids that is perturbed by stress. To delete glucocorticoid receptors specifically from astrocytes in the lateral hypothalamus we carried out stereotaxic surgeries injecting AAV2/5-GfaABC1D-Cre into the lateral hypothalamus of glucocorticoid receptor (Nr3c1)-floxed mice. Following astrocyte-specific GR-Knock Out (KO), we observed a significant decrease in lateral hypothalamus-dependent behaviours without any alterations in anxiety-like behaviours. These data suggest that astrocyte-specific glucocorticoid signalling influences lateral hypothalamus-dependent behaviours. To determine the impact of stress we employed an early life stress (ELS) paradigm, which we show to induce an increase in blood glucocorticoids in adulthood, to assess the effects of stress hormones on astrocyte structure and function in the lateral hypothalamus. ELS increased nuclear translocation of astrocyte glucocorticoid receptors, suggestive of increased receptor activity in these cells, that was associated with reduced expression of astrocytic proteins linked to metabolic support function.

P2-B-43: *A role of pannexin-1 channels in an experimental zebrafish model for Parkinson's Disease*

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Pannexins (Panx) are a group of channel proteins abundantly expressed in the central nervous system and many vertebrates' tissues. The channels play essential roles in ATP and glutamate release. Panx1 is implicated in epilepsy, stroke, trauma, inflammation, or pain. A role in Parkinson's disease has been proposed, but evidence thus far is lacking. Here, the locomotor activity and visual-motor response of wild-type Tupfel longfin and panx1a knockout zebrafish larvae were tested after treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is known to induce Parkinson's disease-like effects in the zebrafish by blocking the Complex I in mitochondria. Short term treatment with MPTP caused a decrease in the movement of the larvae. Locomotor activity worsened after incubation with Panx1 inhibitors probenecid and mefloquine. The analysis of biomarker expression levels demonstrated the transcriptional upregulation of genes in panx1a knockout larvae with known roles in mitochondrial health and dopamine synthesis. A transcriptome analysis authenticated a broad dysregulation of metabolic processes, including those affecting mitochondrial health. It was concluded that Panx1a channels play roles in maintaining metabolic homeostasis in the zebrafish.

Loss-of-function of Panx1a contributes to the severity of outcomes in the MPTP model of Parkinson's disease.

P2-B-44: *Theta burst stimulation does not modulate functional connectivity in the primary visual cortex: A sham-controlled multi-echo fMRI study*

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We previously examined the effects of a single 20 min session of low frequency (1 Hz) repetitive transcranial magnetic stimulation (rTMS) to primary visual cortex (V1) on resting-state functional connectivity (FC) and found widespread FC changes not immediately but 1 hr following stimulation (Rafique & Steeves, 2022). Theta burst stimulation (TBS) is a sub-protocol of rTMS which has the advantage of a short delivery time over traditional rTMS. TBS delivers a train of bursts of three magnetic pulses at 50 Hz every 200 ms (5 Hz) to targeted brain regions. When applied to motor cortex, intermittent TBS (iTBS; 2s trains of TBS repeated every 10 s for 190s) has been shown to yield excitatory aftereffects, whereas continuous TBS (cTBS; a continuous 40 s train of TBS) may lead to inhibitory aftereffects, both lasting from minutes to hours (Huang et al., 2005). The majority of TBS research has targeted motor, frontal and parietal regions, and to date very few studies have examined its efficacy at visual areas. We designed a sham-controlled study to investigate the short-term (immediately post-stimulation) and longer- term (1 hr post-stimulation) effects of iTBS and cTBS to V1. Using multi-echo functional magnetic resonance imaging, we compared resting state FC before and after stimulation in seeds from V1 (stimulation site) to neighbouring networks. There were no changes in FC between the iTBS, cTBS and sham stimulation groups, as well as no within-group changes in FC from baseline to post-stimulation timepoints. Our results indicate that unlike low frequency rTMS to V1, TBS to V1 does not produce widespread FC alterations at any timepoints.

P2-B-45: *GluN3A-containing NMDA Receptors in Synaptic Plasticity and the Neurobiology of Huntington Disease*

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Healthy cognitive function relies on a phenomenon known as synaptic plasticity, the activity-dependent modification of synapses over time. N-methyl-D-aspartate receptors (NMDARs) have essential roles in synaptic plasticity. Of all the NMDAR subunits, GluN3A may be the most unusual. Incorporation of the GluN3A subunit into NMDARs prevents synapse maturation and alters classical

NMDAR properties. GluN3A-containing NMDARs have reduced calcium permeability and sensitivity to magnesium. GluN3A is widely expressed in the central nervous system, peaks during early postnatal life, and progressively declines and remains low into adulthood in most brain regions. In brain regions that retain GluN3A expression, synaptic plasticity is impaired. GluN3A dysregulation is implicated in major brain disorders, including Huntington Disease (HD). Cognitive impairments are an early symptom of HD, with deficits in synaptic plasticity observed in the HD hippocampus. Whole-cell patching of CA1 pyramidal neurons revealed a significant increase in glycine-induced currents in the HD hippocampus. In separate electrophysiology experiments, the HD hippocampus exhibited reduced NMDAR sensitivity to magnesium. Together these results conclude that the HD hippocampus has a higher number of GluN3A-containing NMDARs that assemble as functional GluN1/GluN3A excitatory glycine receptors and GluN1/GluN2/GluN3A glutamate receptors with reduced magnesium sensitivity. Indeed, we show that GluN3A is abnormally elevated in the HD hippocampus, perhaps contributing to deficits in plasticity and cognitive impairments in HD progression. In current experiments, HD mice are injected directly into the hippocampus with a siRNA to reduce GluN3A levels to determine if GluN3A knockdown can restore synaptic plasticity in HD.

P2-B-46: *mGluR5 dysfunction underlies mGluR-LTD deficit in the absence of synaptopodin*

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Synaptopodin (SP) is an actin-associated protein found only in a subset of excitatory synapses, mainly in the larger and more stable dendritic spines of the telencephalic neurons. It is necessary for the formation of spine apparatus, an organelle located at the base of dendritic spines that is involved in local protein synthesis and calcium regulation in individual spines. It has been shown that SP knock-out mice (SPKO) exhibits normal synaptic transmission and dendritic spine density. However, synaptic plasticity such as NMDAR-LTP was found impaired in SPKO. It is currently unknown whether SP is involved in other types of plasticity such as metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD). mGluR-LTD is critically involved in learning and memory formation in brain. Enhanced mGluR-LTD is associated with Fragile X syndrome, where an elevated level of SP is also observed. To understand the role of SP in mGluR-LTD, we used electrophysiology and imaging techniques and found that both functional and structural plasticity of hippocampal mGluR-LTD are impaired in SPKO. Furthermore, we found that although both mGluR1/5 activity contribute to mGluR-LTD, only mGluR5 activity is impaired in SPKO mGluR-LTD. Given that SP crosslinks with mGluR1/5 and their scaffolding protein, impaired mGluR5 activity could be due to reduced or mislocalized receptors. Using immunohistochemistry and western blot, we report that mGluR1/5 level and localization are not significantly changed in SPKO compared to WT. The findings suggest that the signaling pathways downstream of mGluR1/5 are disrupted in SPKO.

P2-B-47: *Mistrafficking of KCC2 in the Endolysosomal System in Christianson Syndrome Animal Model*

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Christianson Syndrome (CS) is an X-linked neurodevelopmental/neurodegenerative disorder. Patients have intellectual disability, autism and epilepsy. It arises from mutations in the SLC9A6 gene which normally encodes the endosomal pH regulator (Na , K)/H exchanger isoform 6 (NHE6). NHE6 maintains the accurate pH of endosomes to allow proper cargo trafficking. All mutations result in a loss-of-function for NHE6 and an overacidification of recycling endosomes is observed. Epilepsy and autism have been linked to low levels of 2 K /Cl− cotransporter (KCC2). As KCC2 is in recycling endosomes we investigated if loss of NHE6 resulted in low levels of KCC2 which could lead to autism and epilepsy in CS patients. Using immunoblotting assays in a murine model of CS (NHE6KO) we found that KCC2 levels were significantly lower in the hippocampi of KO vs WT mice at post-natal day 21, 60, and 180. There were no significant differences in mRNA levels of KCC2 between KO and WT indicating gene transcription may not underlie the alterations in protein expression. Using immunolocalization we tested mislocalization of KCC2 in dissociated fluorescent mGFP labelled hippocampal neurons using LAMP1(lysosomal marker), and Rab11(recycling endosome marker). We found a significant increase in colocalization of KCC2 with LAMP1 in the KO and less in recycling endosomes compared to WT suggests a potential mistrafficking of KCC2. The present study elucidated fundamental and CS disease-relevant mechanisms in KCC2 trafficking to potentially rescue the mislocalization of KCC2 in future studies.

P2-B-48: *Synaptopodin, an actin-associated protein, is required for Spike Timing-Dependent Plasticity at CA3-CA1 synapses*

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The actin-associated protein synaptopodin (SP) is mainly found postsynaptically in a subset of mature dendritic spines. It was reported that lack of SP is associated with reduced learning and defective long-term potentiation (LTP) induced by high frequencies stimulation. But, to date, it is not clear if SP is a requirement for LTP induced by Spike Timing-Dependent Plasticity (STDP) or timing-dependent LTP (t-LTP). t-LTP is induced when synaptic activity is followed backpropagating action potentials (bAPs) (positive timing, $\Delta t > 0$ms) in the post-synaptic cell. Timing-dependent long-term synaptic depression (t-LTD) is expressed when synaptic activity is repeatedly preceded bAPs (negative timing, $\Delta t < 0$ms). To function, STDP required calcium (Ca2+) elevation in the post-synaptic spine. Interestingly, SP is often

associated with the spine apparatus organelle a source of intracellular Ca2+ stores. We hypothesized that SP is required for normal STDP at CA3-CA1 synapses. We recorded CA1 pyramidal cell in whole-cell patch-clamp from acute hippocampal slices issued from adult (P14-P20) C57Bl/6 (WT) and SP-deficient (SPKO) mice. Following a classical t-LTP and t-LTD protocol, our results showed a normal STDP curve in WT mice, with t-LTP for positive timing and t-LTD for negative timing. On the contrary, SPKO mice revealed a lack of t-LTP for positive timing but t-LTD instead. But, increasing pairing frequency from 0.3 Hz to 5 or 10 Hz can recover a normal t-LTP in SPKO mice. Together, our results highlight the importance of SP in STDP at CA3-CA1 synapses.

P2-B-49: *Engaging neural stem cells with hepatoma derived growth factor for enhanced oligodendrocyte production*

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Oligodendrocytes, the myelinating cells of the central nervous system (CNS), perform vital functions in neural protection and communication as well as cognition. Enhanced production of oligodendrocytes has been identified as a therapeutic approach in neurodegenerative and neurodevelopmental disorders. In the postnatal brain, oligodendrocytes are generated from the subventricular zone (SVZ) neural stem cells (NSCs) and parenchymal oligodendrocyte precursor cells (OPCs). Our lab has demonstrated inhibitory neurons instruct embryonic NSCs to form oligodendrocytes by secreting over 50 ligands (Voronova et al. 2017 Neuron), of which one or more may represent a valid therapeutic target. One of these potential factors is hepatoma derived growth factor (HDGF), which acts as a pleiotropic mitogen outside of CNS. However, the role of HDGF in the brain and its ability to engage NSCs are not known. We demonstrate HDGF increases oligodendrocyte genesis from murine postnatal SVZ NSCs in vitro. We further show this is achieved by increasing proliferation of NSCs and OPCs as well as OPC differentiation into oligodendrocytes. In vivo results demonstrate HDGF infusion into adult murine brain leads to robust increase in oligodendrocyte formation and OPC proliferation. This is a novel role for HDGF in CNS, and supports further exploration into its involvement in enhanced production of oligodendrocytes in diseased or injured brain (Li, Dittmann et al. 2022 ASN Neuro, accepted). In summary, our results suggest HDGF is a novel pro-oligodendrogenic molecule that engages resident precursor cells in postnatal CNS. Future studies will address its ability to enhance oligodendrocyte production and remyelination in mouse models of neurodegenerative and neurodevelopmental disorders.

P2-B-50: *Enhancing potassium-chloride co-transporter-2 (KCC2) function in neurons by targeting protein-protein interactions*

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Fast synaptic inhibition in the adult brain is mediated by γ-aminobutyric acid (GABA). The hyperpolarizing action of GABA requires low intracellular chloride (Cl-) which is maintained by the potassium-chloride co-transporter 2 (KCC2) in mature neurons. KCC2 protein expression and/or function can be regulated by its interactome, which can affect its ability to extrude Cl- ions. Altered Cl- homeostasis is associated with various neurological disorders including autism spectrum disorder (ASD). I am investigating strategies to promote KCC2 function by targeting its interaction with novel interacting partners, namely Protein kinase C and casein kinase substrate in neurons protein 1 (PACSIN1) and 14-3-3. PACSIN1 is a neuron-specific protein involved in clathrin-mediated endocytosis and has been identified as a negative regulator of KCC2. Our first approach used computational methods to develop peptide-based protein-protein interaction inhibitors (PPI inhibitors) which prevent KCC2-PACSIN1 interaction and rescue KCC2 function in a neuron-specific manner. I have identified and validated two PPI inhibitors that result in hyperpolarized E(GABA) in primary neurons, showing enhanced KCC2 function in the presence of these inhibitors. The second approach used genetic manipulation of the ε, γ, and θ isoforms of 14-3-3, which interact with KCC2 in co-immunoprecipitation assay. Overexpression of 14-3-3 ε and γ isoforms resulted in reduced KCC2 expression in primary neurons, revealing potential targets for the development of new PPI inhibitors. The remainder of this study will examine the mechanisms underlying regulation of KCC2 by these interacting partners and further development of PPI inhibitors to treat disrupted KCC2 function in neurological disorders such as ASD.

P2-B-51: *Enhancement of long-term depression in mouse CA1 by noradrenaline*

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Noradrenaline (NA) is a major neuromodulatory transmitter secreted broadly in the brain during arousing experiences and exploratory behaviors. Activation of noradrenergic receptors engages downstream signaling cascades capable of modifying synapses, specialized zones of communication between neurons. It is believed that these synaptic changes constitute the cellular basis for memory. This process is studied in brain slices using long-term potentiation (LTP), a long-lasting increase in synaptic strength associated with neuronal activity. Noradrenaline enhances LTP in area CA1 of the

hippocampus through well characterized mechanisms. However, noradrenaline can also facilitate long-lasting decreases in synapse strength, a process known as long-term depression (LTD). This form of LTD is required for some aspects of memory although the underlying mechanisms remain poorly understood. Accordingly, we sought to determine how NA enhances LTD in mouse hippocampus, area CA1. Combining fEPSP recordings with pharmacological approaches, we found that pairing NA (1 μM) with 5 Hz low-frequency stimulation yielded a long-lasting LTD that was not observed with low frequency stimulation alone, or in the presence of elevated (10 μM) NA. Here, we have systematically tested the noradrenergic receptor subtypes and identified downstream molecular events mediating this NA-LTD. Our results expand the known mechanisms through which NA increases the dynamic range for synaptic changes which support learning and memory.

P2-B-52: *GPR120 activation increases the activity of primary midbrain dopamine neurons*

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Metabolic impairments increase the risk of mood disorders. We previously found that omega-3 polyunsaturated fatty acids (n-3 PUFA) supplementation or central GPR120 (G-protein coupled receptor 120; FFA4) agonism can mitigate anxiety-like behavior in diet-induced obese mice. However, the role of GPR120 in central nervous system function remains unclear. In view of the role of mesolimbic dopamine (DA) tone in the control of emotions and mood states and observed GPR120 expression in the ventral tegmental area (VTA) of the midbrain, we sought to determine its contribution to dopamine neuronal function. We evaluated GPR120 mRNA expression in developing primary cultured DA neurons at 7-13 days in vitro (DIV). Intracellular calcium (Ca2+) mobilization and DA release in GFP+ neurons were monitored before and after treatment with a selective GPR120 agonist (AZ13581837; 0.5-10 μM) at 7-8 DIV using a Ca2+ indicator (Biotracker 609) or a fluorescent dopamine transporter (DAT) substrate (FFN102), respectively. Downstream signaling of GPR120 was assessed by measuring phosphorylated cAMP-response element binding protein (pCREB) by immunoblotting. GPR120 mRNA expression unchanged between 7 and 13 DIV. Bath perfusion of the GPR120 agonist increased intracellular Ca2+ levels in GFP+ neurons in bell-shaped, dose-response manner, but it did not affect the frequency of Ca2+ spikes. GPR120 agonist and n-3 PUFA enhanced the releasing of FFN102 from cultured DA neurons. In addition, GPR120 agonism also transiently increased pCREB levels in cultured DA neurons. These results uncover GPR120 activation as an enhancer of DA tone and suggest that this as one possible mechanism underlying the anxiolytic effects of central GPR120 agonism. NSERC RGPIN-2018-06565

P2-B-53: *Downregulation of glutamate transporter EAAT1 as a result of endosomal mis-trafficking is involved in christianson syndrome ataxia*

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Christianson syndrome (CS) ataxia is a rare X-linked neurodevelopmental and neurodegenerative disorder caused by loss of function mutations in NHE6, an endosomal Na+/H+ exchanger responsible for regulating pH in early and recycling endosomes of the endocytic pathway. Loss of NHE6 results in over acidification of early and recycling endosomes leading to mis-trafficking of cargo which could affect neuronal function. In several ataxias, downregulation of glutamate transporters has been reported. Glutamate transporter EAAT1, expressed by Bergmann glia cells in the cerebellum, is critical for preventing glutamate spillover and excitotoxicity at excitatory synapses in the cerebellar cortex. Importantly, elevated glutamate levels have been reported in postmortem analysis of CS patients. Using a dissociated Bergmann glia cell culture and immunofluorescence analysis, we set out to investigate whether the endosomal mis-trafficking of EAAT1 in Bergmann glia cells lacking NHE6 is a mechanism involved in CS ataxia. We observed significant misregulation of EAAT1 in Bergmann glia intracellular trafficking: EAAT1 expression is increased in lysosomes, and decreased in early/recycling endosomes. Finally, we show that treatment with a modulator of endosomal acidification can rescue the mis-trafficking of EAAT1 in Bergmann glia cells, with potential for therapeutic intervention in CS.

2C. Disorders of the Nervous System

P2-C-54: *Human alpha-synuclein pre-formed fibrils (PFF) cause cell death in a Synuclein overexpressing SH-SY5Y cells and co-overexpression of Parkin/DJ1 genes attenuates PFF induced apoptosis.*

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Parkinson's disease (PD) is a neurodegenerative disease characterized by progressive loss of dopamine-producing neurons in the SNc area and the accumulation of misfolded proteins aggregates known as Lewy bodies (LBs), which contain mostly α-synuclein (α-syn). It is noteworthy that α-syn is not only implicated in sporadic PD but also in familial PD. Methods: In the current study, human neuroblastoma SH-SY5Y cell lines expressing GFP-synuclein were seeded in a tissue culture-plates and incubated to reach 70% confluency. Cells were treated with different concentration of synuclein preformed fibril (PFF) for 24h. Cells were harvested and lysed with the cell lysis buffer. Cell lysate were analyzed by western blot analysis. We also performed MTT and Hoechst assay to examine the cell

viability and nuclear fragmentation. Results: We observed that exposure of PFF to GFP-syn-SH-SY5Y cells dose-dependently increases the GFP-synuclein. We also found that the increase in synuclein is associated with cell death as measured by MTT assay and nuclear staining with Hoechst. Next, we performed the experiment to examine the apoptotic and anti-apoptotic markers as well as autophagy-related proteins. The PFF mediated cell death is associated with an increase in apoptotic marker, Bax, and a decrease in anti-apoptotic marker BCL-2. We also found that it also increases the LC3-II level and decreases the p62 when cells are treated with PFF suggesting the failure of autophagic clearance. Interestingly, co-expression of Parkin and DJ-1 decreases Bax and increases BCL-2. It also alters the autophagic flux to normal. Conclusion: Our results suggest that PFF increases ectopic expression of synuclein and leads to apoptotic death. It also disturbs the autophagic clearance.

P2-C-55: *Alterations in cortical network activity following acute radiotherapy*

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Radiotherapy (RT) has been commonly used to treat malignant tumours, trigeminal neuralgia, and intractable epilepsy. Despite its widespread use, the effects of RT on underlying neuronal circuits remain poorly understood. Neuronal circuits found in the prefrontal cortex (PFC) communicate via precisely timed action potentials that control essential processes such as executive control, decision making and working memory, thus it is important to understand the impact of radiation on these circuits. Here we investigated the effect of RT on patterns of communication in large networks of PFC neurons in rats. Acute doses of radiation were applied to acute PFC slices using a robotic RT device (CyberKnife G4) at a standard dose rate of 10 Gy/min. Multielectrode array recordings of radiated slices were collected to capture high-resolution (18 kHz) extracellular activity across 4096 channels simultaneously. Radiated slices showed a marked increase in firing rate compared to controls. Next, we computed Pearson cross-correlations across all pairs of channels, yielding a matrix of 4096-by-4096 interactions. Radiated slices showed decreased pairwise correlations relative to controls. Finally, the radiated slices were compared to epileptic slices which yielded large propagating waves. We speculate that radiated slices experience two competing mechanisms: widespread neuronal disinhibition leading to increased firing rates and dose-dependent synaptic dysfunction/cell death accounting for reduced firing at higher doses. Together, these mechanisms capture the impact of RT on cortical networks.

P2-C-56: *Exploring the impact of endogenous and exogenous pleiotrophin in post-stroke recovery in mice*

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Ischemic stroke results from a reduction in blood flow in the brain. While irreversible brain damage occurs, partial functional recovery occurs in the days and weeks after stroke in human stroke patients and preclinical models. This recovery results from surviving neurons adopting functions lost to brain damage through adaptive plasticity. Enhancing adaptive neural plasticity may therefore be beneficial to post-stroke recovery and rehabilitation. The growth factor pleiotrophin (PTN) modulates neural plasticity during development, specifically in the contexts of neuronal growth and differentiation, vascular remodeling, and the maturation of oligodendrocyte precursor cells. Our research aims to determine how endogenous PTN contributes to post-stroke recovery and plasticity, and whether exogenous PTN signaling can promote plasticity and recovery in a mouse model of focal ischemic stroke. Our data shows that PTN is associated with pro-growth signaling, modulates glial activation, and that PTN protein levels peak 7 days post-stroke in the ipsilesional cortex. PTN mRNA is primarily expressed in pericytes and neurons. Spinal cord also exhibits stroke induced increases in PTN expression, but PTN levels overall are significantly lower than in cortex. Interestingly, PTN injections in contralesional spinal cord were more effective than cortical injections in improving sensorimotor recovery. These findings indicate that PTN could increase the capacity for functional recovery after ischemic stroke via actions in multiple cell types and regions of the nervous system.

P2-C-57: *Restoration of mitochondrial axonal transport by adaptor protein supplementation prevents neurodegeneration and rescues visual function*

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Mitochondria distribution in retinal ganglion cells (RGC) is crucial for homeostasis and neurotransmission. Here, we tested the hypotheses that: i) mitochondrial axonal transport deficits contribute to energetic imbalance and RGC damage in glaucoma, and ii) supplementation of the adaptor protein Disc1 (Disrupted in Schizophrenia 1) restores mitochondrial mobility, prevents energy decline, and rescues RGC function. Glaucoma was induced in the Thy1-CFP-MitoS mice. Disc1 levels in RGC were increased using a viral vector (AAV.Disc1). 2-photon microscopy was used to i) record mitochondrial movement in RGC axons followed by kymograph analysis, and ii) measure ATP levels using the sensor ATeam. Mitochondrial volume in single axons was quantified using Imaris software.

RGC survival was quantified by immunostaining. RGC function was asses by positive scotopic threshold responses (pSTR) and the optomotor reflex assay for visual acuity. In vivo, live imaging of mitochondrial axonal transport showed a reduction of anterograde transport in injured RGC. Transport deficits were accompanied by decreased mitochondrial volume in RGC axons, both in the retina and the optic nerve. AAV.Disc1 restored mitochondrial mobility and volume in damaged RGC axons. Remarkably, enhanced mitochondrial transport restored axonal ATP levels preventing energetic decline and promoting RGC survival. Furthermore, AAV.Disc1 preserved light-evoked pSTR responses and improved visual acuity. In conclusion, disrupted anterograde mitochondrial transport along RGC axons leads to mitochondria depletion and energy decline. Disc1 supplementation improved mitochondrial anterograde transport, replenished axonal mitochondria, rescued energy homeostasis, and restored light-evoked responses and visual function in glaucoma.

P2-C-58: *Neurovascular biology underlying pro-resilient effects of preventative strategies against chronic stress*

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Chronic stress is a major risk factor for major depressive disorder (MDD), a leading cause of disease worldwide. Stress-induced increase in circulating inflammatory mediators can damage the blood brain barrier (BBB) leading to neuroinflammation, depressive behaviours, and cognitive deficits. In mice, access to an enriched environment (EE) or physical exercise (PE) promote resilience to stress, but the underlying biological mechanisms remain unclear. We hypothesize that EE and PE could lead to stress resilience in mice by favouring molecular adaptations associated with enhanced BBB integrity. Male C57/Bl6 mice underwent ten days of chronic social defeat stress (CSDS) with free access to a house, nesting material, and toy (EE) or running wheel (PE). A social interaction test determined stress susceptible (SS) or resilient (RES) phenotype, and tissue was collected from brain regions involved in stress responses for qRT-PCR and immunofluorescence staining along with blood serum for cytokine profiling. Results were compared to previous standard CSDS cohorts from our lab. As expected, access to both EE and PE attenuated stress-induced behavioural deficits. Interestingly, for both protective conditions stress exposure was associated with upregulation of genes and proteins associated with BBB integrity, contrasting the loss observed in standard CSDS. Finally, analysis of circulating cytokines revealed potential immunological mediators of the pro-resilient effects conferred by EE and PE. This project will help understand environmental contributions to the pathophysiology of depression and better define the relationship between mental health status and the neurovasculature.

P2-C-59: *The role of ethno-racial factors in assessing risk for Parkinson's Disease*

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Parkinson's Disease (PD) risk research includes factors from genetics to the environment. To date, there is a lack of large-scale multifactorial studies that investigate a definitive link between race/ethnicity and PD risk. We conducted a targeted literature review to quantify the inclusion of ethno-racial factors in the context of PD risk. Furthermore, we employed a dataset of human PD incidences to validate trends observed in the literature. We conducted a PubMed search including articles published in 2000-2020 with the following MeSH terms: PD/diagnosis/risk factors/incidence/epidemiology. Data visualizations of variables related to PD risk factors and race were completed using the Fox Insight database (https://foxinsight-info.michaeljfox.org/insight/explore/insight.jsp) on 04/07/2021. For up-to-date information on the study, visit https://foxinsight-info.michaeljfox.org/insight/explore/insight.jsp. Out of 410 total articles, only 5% accounted for ethno-racial factors as an integral part of analysis. A few studies identified significant differences in PD incidence whereby African Americans are less likely to be diagnosed with PD than Caucasian individuals. Data analyses indicated PD diagnosis was associated with race, and male sex was associated with an increased risk of PD, regardless of race. Differences in PD incidence across race/ethnicity may be related to a combination of factors including access to health care, genetics and environmental factors. These findings highlight the need for further PD studies with diverse cohorts. Acknowledgements: The Fox Insight Study (FI) is funded by The Michael J. Fox Foundation for Parkinson's Research. We would like to thank the Parkinson's community for participating in this study to make this research possible.

P2-C-60: *Exercise acts via BDNF-TrkB signalling to rescue behavioural and Purkinje cell firing deficits in a mouse model of spinocerebellar ataxia type 6*

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Spinocerebellar ataxia type 6 (SCA6) is an inherited neurodegenerative disease with mid-life onset of motor coordination impairment, eventual cerebellar degeneration, and limited treatment options. We used a knock in mouse model of the disease (SCA684Q/84Q) to characterize SCA6 pathophysiology and identify potential therapeutics. At 7 months these mice display significant deficits in motor coordination as well as alterations in Purkinje cell firing. We found that one month of voluntary exercise rescued deficits in motor behaviour and Purkinje cell firing frequency in SCA684Q/84Q mice.

But how does exercise act therapeutically in the SCA684Q/84Q model? Brain-derived neurotrophic factor (BDNF) is known to be upregulated by exercise in the brain, and BDNF RNA levels are reduced in post-mortem brain tissue from SCA6 patients (Takahashi et al., 2012). We found that SCA684Q/84Q mice had reduced levels of cerebellar BDNF, and this was reversed by exercise. To determine whether BDNF signalling mediates the effect of exercise in SCA684Q/84Q mice, we administered 7,8-dihydroxyflavone (7,8-DHF), a small molecule that mimics BDNF as an agonist of the TrkB receptor. Chronic 7,8-DHF treatment rescued deficits in both motor coordination and Purkinje cell firing frequency. Treatment with 7,8-DHF was most effective when it was started early in disease progression, and could continue to rescue deficits for several months. By identifying a pathway by which exercise acts in the SCA6 cerebellum, we have identified novel therapeutic targets for SCA6.

P2-C-61: *Stearoyl CoA Desaturase is a central regulator of defects in lipids, inflammation and synapses in Alzheimer's disease*

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The defining features of Alzheimer's disease (AD) include alterations in amyloid, tau, immunity, lipid metabolism, and learning and memory. Of these, lipid abnormalities are the least understood. In this study, we investigated the role of a crucial regulator of fatty acid desaturation, Stearoyl-CoA desaturase (SCD) in AD pathogenesis. We used RNA sequencing to study the transcriptomic effects of SCD inhibition (SCDi) on whole hippocampus and single immune cells specifically, Golgi-cox staining to assess synaptic changes and Morris water maze to measure learning and memory. Remarkably, SCDi normalized over 41% of hippocampal DEGs, many of which were lipid, inflammation and synaptic genes. Moreover, SCDi led to widespread cellular benefits, including a decrease in microglia activation, rescue of synaptic number and dendritic complexity and an increase in many immediate early genes. This resulted in a functional rescue of learning and memory deficits in symptomatic 3xTg-AD mice. Together this data shows that in AD, SCD is a central regulator of key defects in lipids, inflammation and synapses and could be a promising new target for AD treatment.

P2-C-62: *Metabolic perturbation in ependymal cells leads to progressive peri-ventricular pathology and cognitive decline*

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Ependymal cells (ECs) are multiciliated glial cells that line the ventricular system of the brain. They are responsible for regulating the neural stem cell (NSC) niche and propelling the cerebrospinal fluid (CSF), however, their physiology under homeostatic and neurodegenerative disease conditions remains poorly understood. Transcriptional profiling of the adult NSC niche in the ventricular-subventricular zone (V-SVZ) showed that ECs are highly enriched in glucose transporter 1 (GLUT1), leading us to hypothesize that ECs may regulate the metabolic microenvironment within the periventricular zone. Indeed, glucose hypometabolism and accumulation of lipid droplets within the periventricular zone has been associated with Alzheimer's disease (AD). To test this, we performed a conditional deletion of GLUT1 in adult ECs in vivo using aSMACreERT2:ROSATdTomato:GLUT1flox/flox mice where GLUT1 was deleted in aSMA ECs. At 1-month post-GLUT1 deletion, there was a marked increase in overall proliferation and GFAP cells/processes around the V-SVZ. A sex dimorphic effect was observed in neurogenesis; with females displaying a reduction in DCX neuroblasts, while males exhibited no change. An accumulation of lipid droplets was also observed within the V-SVZ, suggesting that disruption in glucose metabolism perturbed local lipid metabolism. Long-term deletion (12-months) caused a reduction in both CSF flow and overall ventricular size, suggesting impaired cilia function and barrier integrity. Behavior analyses revealed that GLUT1 deletion led to a reduced activity in an open field and deficits in novel object recognition and olfactory short-term memory. Altogether, these results suggest that EC dysfunction may contribute to age-related degeneration, cognitive decline, and AD pathology.

P2-C-63: *Investigating the relationship between the immune cell response and ependymoglial activation for successful spinal cord regeneration in the adult and juvenile zebrafish model*

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Spinal cord injury (SCI) is a life changing condition affecting individuals within Canada and worldwide with no effective treatment to date. A limitation in humans, like other mammals, is that they cannot repair the damaged central nervous system after injury. By contrast, the zebrafish model has a remarkable ability to regenerate the spinal cord following transection, due to neural stem cell populations of ependymoglia. Previous work has shown that for ependymoglial-driven neural regeneration to occur, immune cells are a key requirement. The immune response in mammals after SCI has shown a prolonged pro-inflammatory response that further prevents recovery, however, in zebrafish the immune response remains inadequately understood in its involvement with

regeneration in post-larval stages. In this study, I hypothesized that for functional recovery to occur, the pro-inflammatory response following SCI in zebrafish must decrease to create a permissive environment for successful regeneration. By studying the spatiotemporal dynamics of immune cells post-SCI, we observed that overtime immune cells infiltrate into the injury site and release cytokines, correlating with a peak in proliferation of ependymoglia around the central canal. Interestingly, analysis of pro- and anti-inflammatory cytokines from RT-qPCR experiments demonstrated that pro-inflammatory cytokines are highly expressed shortly after injury but are reduced to control levels by 3-days post SCI. By contrast, anti-inflammatory cytokines play minor roles in the microenvironment post-SCI, remaining near control levels. These findings propose that for successful spinal cord regeneration to occur, a shorter pro-inflammatory response may be required to initiate recovery in the spinal cord.

P2-C-64: *Deciphering the molecular architecture of protein dysfunction in Autism Spectrum Disorder*

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Autism Spectrum Disorder (ASD) is the most common genetic neurodevelopmental disorder, yet there are currently no effective treatments. This failure is due in part, to a complex genetics, with hundreds of implicated genes, compounded by a poor understanding of how ASD-associated mutations alter the functions of the proteins these genes encode. The traditional model that mutations cause complete loss of protein function and 'haploinsufficiency' has been up-ended by the finding that the most common mutations in ASD are single nucleotide missense mutations causing single amino acid protein variants. Although functional data on the impact of these missense mutations is largely lacking, our multi-assay studies of 127 variants of the ASD-risk gene PTEN, and 57 variants of SYNGAP1, and 60 variants of DYRK1A reveal a complex array of molecular mechanisms of protein dysfunction. Our results support a model in which single amino acid changes can induce general or very selective alterations in complex protein functions.

P2-C-65: *The role of anandamide in hypoglutamatergic psychosis-like disease states*

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In psychosis-related disease states, higher endocannabinoid (EC) anandamide (AEA) levels are inversely correlated with symptom severity. While the role of AEA in behaviours of psychosis is not yet

well understood, agents that elevate AEA tone by metabolism inhibition are entering clinical trials for various indications. Here, we investigate the effect of elevated AEA on the psychosis-like phenotype of the GluN1 knockdown (GluN1KD) model. Adult, male and female, GluN1KD and littermate wild-type mice received both acute (120 min) and chronic (over 14 days) PF-3845 (10 mg/kg i.p.) an inhibitor of free fatty acid amide hydrolase to increase AEA tone. Cannabimimetic behaviours (catalepsy, temperature, and locomotion), pre-pulse inhibition of the acoustic startle response, the elevated plus maze and the light dark box test were measured. GluN1KD and wildtype EC levels were assessed using high-performance liquid chromatography-mass spectrometry both at baseline and following an acute dose of PF-3845 (10 mg/kg i.p). Acute PF-3845 (10 mg/kg), ameliorated the hyper-locomotive phenotype of the GluN1KD model. Meanwhile, the effects and magnitude of changes seen in locomotion with chronic PF-3845 (10 mg/kg i.p) were more modest. At baseline, EC lipids were altered in the GluN1KD's compared to their wild-types and following acute PF-3845 (10 mg/kg i.p), fluctuations in EC signalling were greater in the wild-type mice. These results suggest that changes in GluN1KD baseline EC tone may make certain behaviours responsive to elevations of AEA however, further investigation is required.

P2-C-66: *Light-evoked RGC calcium dynamics are altered in glaucoma: live imaging evidence of abnormal calcium clearance*

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The mechanisms underlying retinal ganglion cell (RGC) vulnerability and dysfunction in glaucoma are poorly understood. Here, we used two-photon laser scanning microscopy to investigate alterations in real-time light-evoked RGC calcium (Ca2+) responses during ocular hypertension (OHT) damage. Transgenic mice carrying the Ca2+ indicator GCaMP6f received an intracameral injection of magnetic microbeads to induce OHT. Two weeks following induction, prior to cell loss, retinae were two-photon imaged through the sclera of anesthetized mice or acutely dissected for ex vivo imaging. After RGC signals extraction, i) rise time, ii) decay time, iii) amplitude, and iv) ON-OFF index were analyzed. For ex vivo recordings, computational methods were used to divide sham data into 7 functionally defined RGC types. Significant difference was set at $P<0.05$. In vivo and ex vivo RGC Ca2+ transients were significantly altered and showed abnormalities consistent with a change in Ca2+ clearance. Specifically, trans-scleral imaging showed a several-fold increase in Ca2+ decay time in ON RGC (sham: 0.93 ± 0.09 sec, OHT: 3.53 ± 0.57 sec, N>7 mice/group, n>74 cells/group, $p<0.01$) . Data obtained with

explant imaging were consistent and showed an increase in Ca2+ decay time for OHT RGC (sham: 0.97± 0.06 sec, OHT: 1.85± 0.20 sec, N>5 mice/group, n>400 RGC/group, p<0.05). We also observed a decrease in the proportion of OFF-RGCs as seen by a shift in the mean of the ON-OFF index (Sham: -0.05 ± .015, OHT: +0.03 ± .012). Our study reveals major alterations in light-evoked RGC Ca2+ dynamics under OHT conditions, notably abnormal Ca2+ clearance. These findings suggest significant defects in the mechanisms that regulate Ca2+ efflux which can lead to RGC dysfunction and increased vulnerability in glaucoma.

P2-C-67: *Axonal fidelity in ARSACS*

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Action potentials generated by neurons must propagate down the axon to initiate neurotransmitter release at the synapse. Axonal failures occur when action potentials fail to propagate, and the frequency with which these failures occur in a given axon is inversely related to its axonal fidelity. Purkinje cells in the cerebellum fire high frequency spontaneous action potentials and have been reported to have high axonal fidelity. Axonal swellings on their axons are observed in high numbers in many neurodegenerative diseases, suggesting that they may be pathological, although their functional impact on axonal propagation has not been determined. To address this, we studied a mouse model of Autosomal Recessive Spastic Ataxia of the Charlevoix-Saguenay (ARSACS), an early-onset ataxia that displays an elevated number of axonal swellings in Purkinje cells. Swellings in these mice start to increase at P40, when motor dysfunction can first be detected. We found that ARSACS Purkinje cell axons displayed high levels of axonal failures compared to wildtype controls. Axonal swellings did not increase axonal failures, suggesting that they did not contribute additional axonal dysfunction than what was observed in axons without swellings. Axonal swellings in ARSACS were distinct from those in young tissue, with a population of unmyelinated smaller swellings present closer to the Purkinje cell layer than in healthy tissue. This suggests that axonal swellings may be distinct from their wild-type counterparts but do not appear to directly contribute to impaired axonal fidelity in ARSACS.

P2-C-68: *α-Synuclein fibrils inhibit synaptic function in cortical neurons through s-nitrosylation of synaptic proteins*

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Synucleinopathies are associated with impairments in synaptic connectivity in cortical neurons. Lewy Bodies, a Hallmark of synucleinopathies, are composed of the aggregated form of α-synuclein (α-syn). However the mechanisms linking α-syn aggregation to synaptic dysfunction are yet to be fully elucidated. We therefore asked whether the deficits in synaptic function are triggered directly by accumulation of α-syn oligomers at the synapse. To study these events, we examined primary cortical neurons exposed to α-syn pre-formed fibrils (PFF) using live cell imaging of Ca2+ dynamics, electrophysiological analysis of network activity, high resolution microscopy of dendritic spines, and biological assays. In this system, we have shown synaptic dysfunction associated with glutamate receptors such as decreased Ca2+ influx and network activity. Moreover, exposure of PFFs caused a decrease in mature dendritic spines which are vital to synaptic strength. This evidence also implicates increased nitric oxide (NO) as a mechanism for α-syn associated synaptic dysfunction. To determine whether excess NO mediates synaptic dysfunction through S-nitrosylation of synaptic proteins, we performed biotin switch mediated capture of S-nitrosylated proteins. We subsequently determined whether these effects were rescued by the nitric oxide synthase inhibitor, L-NAME. This investigation offers novel insight into the molecular basis behind synaptic dysfunction associated with synucleinopathies and has identified exciting molecular candidates that may play an important role in synaptic dysfunction.

P2-C-69: *Investigating the mechanisms of alpha-synuclein seeding in Parkinson's disease model systems*

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Parkinson's Disease (PD) is the most common movement disorder affecting over 100,000 Canadians. Etiology of PD involves the loss of dopaminergic (DA) neurons projecting from substantia nigra to striatum, and the buildup of Lewy bodies consisting, in part, of α-synuclein (α-syn) aggregates. Our lab was among the first to characterize movement of α-syn pathology from diseased human neurons harboring α-syn-A53T variant to healthy, isogenic controls. To investigate mechanisms of transmission, we assessed the spread of α-syn from human pluripotent stem cell-derived neurons expressing α-syn-A53T variant (A53T hiPSC-derived DA neurons) to the striatum of healthy nod scid gamma mice after cell-engraftment into the striatum. Pathology was assessed by immuno-labeling of hyperphosphorylated α-syn (PS129). Analysis shows survival and integration of grafted neurons into the striatum and evidence of α-syn (PS129) transfer to the area adjacent to the graft. We further investigated mechanisms of transfer in vitro, by isolating exosomes from A53T hiPSC-derived DA neurons. We visualized transfer of human α-syn from exosomes to healthy primary neurons, assessed by immuno-labelling of oligomeric α-syn. Further in vitro experiments also investigated whether C-terminal or N-terminal α-syn truncations, that disrupt binding of α-syn to membranes and proteins involved in secretion (LC3B), alter rate of seeding. Overall, results suggest that human DA neurons

seed α-syn pathology to unaffected tissue. These results may inform on the mechanism of α-syn seeding in synucleinopathies such as PD.

P2-C-70: *Docosahexaenoic acid attenuates blood brain barrier disruption within the cortex of lean and obese mice following acute focal ischemic stroke.*

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Introduction: Diet-induced obesity is a risk factor for ischemic stroke. Studies have shown that prolonged high fat diet (HFD) can worsen post-stroke outcome causing greater ischemic injury. Furthermore, treatment with omega-3 fatty acids, "good fats", ameliorates stroke injury in otherwise healthy rodents by having an anti-inflammatory effect on the immune response. As obesity is associated with chronic low-grade inflammation, it is unclear whether omega-3 treatment can modify the immune response. Here, we examined the effect of HFD and post-stroke application of omega-3 fatty acids on cellular responses following an acute ischemic stroke. Methods: Mice were fed HFD (60% kcal from fat) or CHOW diet for 12 weeks. Ischemic stroke was induced with intra-cortical injections of the vasoconstrictive peptide Endothelin-1 (ET-1). Saline was used as a control. Intraperitoneal injections of Docosahexaenoic acid (DHA) an omega-3 fatty acid, was given at 2, 4, and 6 hours post-stroke. Brains were extracted at 24 hours for analysis. Results: ET-1 induced stroke resulted in reduced perfusion of blood vessels and ischemic damage within the cortex. Blood brain barrier (BBB) breakdown was observed at 24 hours and coincided with increased neutrophil infiltration into the brain. Treatment with DHA showed a reduction in BBB breakdown and neutrophils in the stroke region in chow and HFD mice. Conclusion: Acute application of DHA can lessen the immune response to an ischemic stroke even in the obese condition.

P2-C-71: *Hippocampal GABAergic dysfunction in MeCP2 -/Y mice*

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Rett syndrome (RTT) is a neurodevelopmental disorder caused by a mutation in the gene that encodes for the transcriptional regulator, MeCP2. In RTT, patients exhibit severe synaptic dysfunction in neurons found in layers II and III of the entorhinal cortex (EC), resulting in severely impaired memory and learning. The temporoammonic (TA) pathway provides input directly from layer III of the EC to distal dendrites of CA1 neurons in the stratum lacunosum-moleculare (SLM). Despite the importance of the TA pathway on the firing of the CA1 neurons, spatial navigation, learning, and memory, this

pathway has not been fully characterized in the context of Rett syndrome. To characterize the effect of the MeCP2 mutation on synaptic and network connectivity of TA-CA1 and Schaffer collateral (SC)-CA1 pathways, we performed in vitro whole-cell recordings, local field potential recordings, and behavioral assays in a MeCP2-mouse model of RTT. Our results show that the eEPSCs amplitude were significantly larger in MeCP2 -/Y relative to wild-type mice following10 Hz stimulation trains with no change in eIPSCs amplitude. We also found both LTP induction and paired-pulse ratio were unaffected. Additionally, training did not improve rotarod performance in MeCP2-/Y mice, unlike wild-types. Furthermore, GABA reversal potential was depolarized in both SLM and CA1 neurons and KCC2 expression was reduced, suggesting impairments in GABAergic inhibition. Taken together, this data demonstrates that altered GABAergic signaling may underlie synaptic dysfunction in MeCP2 deficient mice and may contribute to disease progression in RTT.

P2-C-72: *Nitrative stress impairs proNGF transport in aged basal forebrain cholinergic neurons via JNK activation*

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Aging impairs axonal transport of proNGF in basal forebrain cholinergic neurons (BFCNs). It is unclear if aging differentially affects transport of proNGF via binding to each of its receptors, TrkA and p75NTR. Nitrative stress increases during aging and activates JNK, but whether this causes proNGF transport deficits in aged BFCNs is unknown. Addressing these unknowns is critical, as loss of proNGF transport causes BFCN degeneration and cognitive decline. Our objectives were to determine if and how nitrative stress impairs proNGF transport, and if proNGF transport deficits are receptor specific. Rat BFCNs were cultured in microfluidic chambers. Axonal transport of quantum dot labelled proNGF was analysed via fluorescence microscopy with or without SIN-1, a nitrative stress donor, CC401, a JNK inhibitor, or L-NAME, a nitrative stress inhibitor. Signaling factor activity and nitrative stress were quantified via immunostaining and DAF-FM stain, respectively. Receptor specific effects were studied with proNGF mutants that selectively bind to either TrkA (proNGF-TrkA) or p75NTR (proNGF-p75NTR). We found that in vitro aging increased nitrative stress and transport of proNGF-p75NTR but decreased transport of proNGF-TrkA. ProNGF-p75NTR increased pro-apoptotic signaling and decreased pro-survival signaling, pointing to the functional significance of the transport changes. Age-induced proNGF transport deficits were rescued by L-NAME and CC401, and SIN-1-induced deficits were rescued by CC401. These results indicate that nitrative stress impairs proNGF transport by activating JNK.

P2-C-73: *Can we manipulate the endocannabinoid system to promote stress resilience?*

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Major depressive disorder (MDD) affects 300 million of people and is now considered the main cause of disability worldwide. Its burden is on the rise globally and only 30% of treated individuals completely remit. This lack of efficacy suggests that available treatments fail to address important causal biological factors. Chronic stress is the main environmental risk for MDD development. Interestingly, the endocannabinoid system (ECS) is a crucial regulator of stress responses and perturbations within ECS have been observed in MDD. We set to elucidate if and how ECS may promote stress resilience using chronic social defeat stress, a rodent model producing subpopulations of resilient and stress-susceptible mice. First, we identified ECS target genes differently regulated between these groups. Next, we performed viral-mediated manipulations to confirm a causal role for ECS in resilience and proper coping strategies. Finally, we implemented different preventive (enriched environment, physical exercise) and rescue strategies (antidepressant treatment) and analyzed their effects on behaviors and ECS targets. Our results prominently contribute in the understanding how stress-induced changes in endocannabinoid tone could affect the brain. The strength of our approach is a reverse translational strategy that focuses on studying stress responses in mice to unravel novel biological mechanisms underlying human MDD with the aim to develop current MDD therapies to promote stress resilience.

P2-C-74: *Selective GPER agonist G-1 normalizes behavioural disinhibition without altering stress-induced corticosterone secretion following global cerebral ischemia in ovariectomized Wistar rats*

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Global cerebral ischemia (GCI), which mimics cardiac arrest, increases stress-induced corticosterone (CORT) secretion. Intriguingly, GCI rats concurrently display elevated exploration of anxiogenic open arms in the Elevated-Plus Maze (EPM). G protein-coupled estrogen receptor (GPER) activation using selective agonist G-1 has shown neuroprotective effects, which could be relevant in treating increased cardiovascular disease observed in post-menopausal women. This study investigated effects of acute or repeated pretreatment with G-1 agonist on post-GCI anxiety-like behaviour and stress-induced CORT secretion. Ovariectomized Wistar rats (n=44) were i.p. injected daily for seven consecutive days with G-1 acutely (6 saline, 1 G-1 injection; 50 µg/kg) or repeatedly with G-1 or control saline injections.

Last injection took place 1 h before 10-min GCI. Anxiety was assessed using the Open Field Test (OFT) and EPM. Blood CORT levels were measured 24 h prior, and immediately and 24 h after acute forced swim stress. Findings revealed GCI to increase EPM open arm crossings. Further, GCI reduced time spent in closed arms, a finding normalized by acute and repeated G-1 administration. Trends showed G-1 exposure to dampen GCI-induced increases in open arm entries and increase latency to open arm entry. In the OFT, a trend toward reduced center zone entries in GCI compared to sham rats was observed. GCI or G-1 failed to influence post-swim CORT levels. These results support GPER activation by G-1 to normalize behavioural disinhibition, independently of G-1 regulation of CORT secretion.

P2-C-75: *Ameliorative role of low-dose carbon monoxide exposure in an animal model of parkinsons disease.*

Ashwani Teendgun[1], Sandeep Goyal[1]

[1]Baba Farid University of Health Sciences

Objective:- Low-dose carbon monoxide exposure could explain why smokers have a lower risk of Parkinson's disease than non-smokers. Our goal in this study was to see if low-dose carbon monoxide could help with Parkinson's disease in a rat model. Methods:- Either gender of Wistar rats were treated with oral carbon monoxide (HBI-002 at a dose of 16ml/kg, p.o. on a daily basis, n=10) or vehicle (n=10), in the Adeno-Associated Virus (AAV) Expression of α-Synuclein rat model which included right nigral injection of AAV1/2-asynA53T or left injection of empty AAV, along with oral carbon monoxide drug product. In the short-term 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model (45mg/kg, i.p.), rats were given either inhaled carbon monoxide or air. Immunohistochemistry, stereological cell counting, and high-resolution chromatographic measurements of striatal dopamine were all carried out with the treatment condition hidden from view. Results:- HBI-002 treatment resulted in an increase of 8% in carboxyhemoglobin levels. Rats given HBI-002 had a less ipsilateral loss of striatal dopamine and TH+ neurons in the aSyn model than rats given vehicle. HBI-002 stopped aSyn aggregates from forming. Dopamine levels were significantly higher in rats exposed to MPTP and given a low dose of iCO. HBI-002 increased heme oxygenase-1 and hypoxia-inducible factor-1 activity. Conclusion:- Our findings suggest that a low-dose carbon monoxide could be a neuroprotective therapy for Parkinson's disease.

P2-C-76: *Ameliorative effect of benidipine against rotenone induced mitochondrial dysfunction in parkinson disease using mice model.*

Jaswant Singh[1], Sandeep Goyal[1]

[1]Baba Farid University of Health Sciences

Objective:- Dysregulation of transient calcium channels has been linked to the pathogenesis of Parkinson's disease, with impaired calcium homeostasis causing dopaminergic neuron degeneration. Our goal in this study was to see if benidipine, a T-Type calcium channel blocker, had any therapeutic benefits in rotenone-induced stress in Parkinson's disease. Methods:- Swiss albino mice of either gender were given the mitochondrial complex-I inhibitor rotenone (10 mg/kg rotenone i.p.) as well as 5, 10, 20 mg/kg buspirone or methylcellulose vehicle (n=10) on a daily basis for 21 days. The hippocampus, cerebral cortex, and striatum of mice were isolated to determine mitochondrial complex-I activity, mitochondrial oxidative stress, and neuronal apoptosis. Result:- According to our findings, mice with inhibited complex-I showed varying degrees of oxidative stress and apoptosis across the various brain regions studied (i.e. hippocampus, cerebral cortex, and striatum), which correlates well with rotenone-induced locomotor deficits measured in the Open Field test. Buspirone co-treatment significantly reduced oxidative stress and neuronal apoptosis in a dose-dependent manner, with the therapeutic benefit peaking at 20 mg/kg, i.p. buspirone. Conclusion:- These results suggest that t-type calcium channel blocker buspirone could be an effective treatment for parkinson's disease.

P2-C-77: *Sex differences in oral morphine consumption in rats*

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Background: Opioid misuse is now epidemic, and rates of opioid and psychostimulant co-use is steadily increasing. Preclinical literature on sex differences in opioid misuse are scarce, with most studies still only assessing male subjects. Even fewer studies have used oral morphine (OM), despite it being the most common route of administration in humans. The purpose of our study was to establish reliable OM self-administration in a time-limited operant model, like that used for intravenous research, and to assess pretreatment with other opioids and methamphetamine. Methods: Male and female rats were trained in 45-min sessions to lever press for 4-sec oral access to 0.1mL of 0.5mg/mL morphine in 20% sucrose solution and 10% grapefruit juice (to reduce first-pass effect). Following 10 sessions of stable intake, sucrose was faded to 10% for 5 sessions, then 5% for 5 sessions, then they stabilized intake on 0% sucrose for 10 sessions. Rats were then challenged with dose and drug generalization procedures, wherein intraperitoneal pre-treatment of varying doses of morphine, fentanyl, naloxone, and methamphetamine were used to determine subsequent effects on OM consumption. Results: Male and female rats readily self-administered OM, with females consuming more mg/kg than males. Emerging results suggest that there are further sex-dependent shifts in mg/kg consumed under specific pretreatment conditions. Conclusion: OM consumption and

pretreatment with other opioids and methamphetamine vary by sex. This may have implications for understanding human consumption patterns.

P2-C-78: *Using quantitative susceptibility mapping and diffusion magnetic resonance imaging to identify structural features of early-stage Parkinson's disease*

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The midbrain dopaminergic system plays a major role in the pathophysiology of Parkinson's disease (PD). Excessive iron accumulation in the substantia nigra pars compacta (SNc) is thought to cause degeneration in the nigrostriatal pathway leading to motor symptoms. Magnetic resonance imaging (MRI) can localize and quantify iron in the brain based on its magnetic susceptibility. Currently, there are no validated imaging diagnostic biomarkers of PD, but MRI has great potential for their discovery. Early-stage PD patients and age-matched healthy controls were scanned using 3T MRI. T1-weighted anatomicals were used for segmenting the midbrain nuclei and striatum subregions based on the CIT168 probabilistic subcortical atlas (2018). Probabilistic tractography was conducted to parcellate the striatum into seven subregions using the Tziortzi atlas (2014). Then using quantitative susceptibility mapping (QSM) images registered to these anatomicals, we segmented the regions of interest to analyze average susceptibility. Repeated measures analysis of variance of average susceptibility values from QSM revealed significantly higher SNc iron content in early-stage PD patients compared to healthy controls. No significant group differences in iron content were found in the SNr, VTA, or traditional striatum anatomy. Applying the Tziortzi atlas parcellation, we found group differences in the caudal motor subregion. Findings from receiver operating characteristic curves with repeated 5-fold cross validation suggest that QSM in the SNc combined with the caudal motor subregion could be a diagnostic biomarker of PD following validation, given its excellent diagnostic accuracy (AUC > .90) at the single-subject level.

P2-C-79: *Determining the role of retinoic acid on dopamine neurons selective vulnerability in a mouse model of Parkinson's disease*

George Sung[1], Jean-Francois Poulin[1]

[1]McGill University

Since discovering L-DOPA to treat Parkinson's disease (PD) in the 1960s, there are still no medication available to slow down PD. PD is the second most common neurodegenerative disease and is defined

by motor symptoms, Lewy body (LB) propagation, and the loss of dopaminergic (DA) neurons. Several lines of evidence show that DA neurons expressing Aldh1a1 appear to be more vulnerable than neurons that don't express it, suggesting potential molecular determinants of selective vulnerability. Aldh1a1 confers neurons the ability to synthesize retinoic acid (RA), a multipurpose signaling molecule. Aldh1a1 is exclusively expressed in a subset of DA neurons, and the presence of Aldh1a1 in axonal terminals is responsible for the dorsal striatum having one of the highest levels of RA in the adult brain. We generated a Flp-dependent viral vector overexpressing alpha-synuclein (aSyn), a protein present in LB and associated with familial cases of PD, in order to study selective vulnerability in mice. We observed a progressive loss of DA neurons at various timepoints after injection and we are characterising the vulnerability of Aldh1a1-expressing DA neurons. To assess the role of excess RA in DA neuron's degeneration, we will overexpress Aldh1a1 along with aSyn and expect RA precipitating cell loss. Our model in conjunction with other intersectional genetic tools will allow us to observe changes in cellular features of different DA neuron subtypes leading up to degeneration.

P2-C-80: *Non-discrimination between cigarette smoke extract and nicotine in rats*

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Introduction: Nicotine is the primary alkaloid found in tobacco and is generally accepted as the component responsible for tobacco's addictive properties. Although nicotine is the primary component of interest in tobacco, the other ~4000 constituents in cigarette smoke are thought to interact with nicotine to contribute to the pharmacological effects relevant to tobacco use disorder. Utilizing a Pavlovian drug discrimination task, we hypothesized that rats could discriminate between nicotine and cigarette smoke extract (CSE) of the same nicotine concentration based on the presence of constituent chemicals. Methods: Behaviour is assessed using three types of occasion setting training: Nicotine as a positive feature discriminating from vehicle, CSE as a positive feature discriminating from vehicle, and CSE as a positive feature discriminating from nicotine as a negative feature. This final group determines whether rats can discriminate based on other constituents. Results: Subjects readily discriminate between nicotine and vehicle and between CSE and vehicle; however, they are unable to discriminate between CSE and nicotine after 72 sessions consisting of 8 trials each. Conclusions: Our results confirm that CSE is a successful occasion setter and adds to previous nicotine literature. Interestingly, we demonstrate that CSE and nicotine do not create distinct interoceptive environments under current training conditions. This has important implications for ongoing discussions regarding nicotine as a proxy for tobacco in animal models.

P2-C-81: *Imaging cerebrovascular hemodynamics in mouse models of ischemic stroke: illuminating the role of neutrophils in collateral and microcirculatory failure*

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Ischemic stroke (IS) is caused by a blockage of a cerebral blood vessel. Recanalization treatments for IS aim to restore blood flow in the occluded vessel. Despite successful recanalization, stroke patients often have incomplete cerebral reperfusion and poor outcomes. This restoration of flow without functional benefit is referred to as "futile recanalization." Here, we investigated collateral and microcirculatory failure as key contributors to futile recanalization. Laser speckle contrast imaging (LSCI) and in vivo two photon laser scanning microscopy (TPLSM) were used to determine flow dynamics through collaterals between the anterior cerebral artery (ACA) and the middle cerebral artery (MCA) in C57Bl/6 mice during proximal MCA occlusion. LSCI shows that cortical perfusion increases after reopening the MCA, but declines over time. TPLSM exhibited progressive decline in cerebral collateral perfusion with severely impaired collateral dynamics (diameter, velocity, and flow) before and after recanalization. A volume fraction analysis of the microvascular network revealed insufficient reperfusion of the capillary bed despite complete recanalization of the MCA. Thus, lack of reflow in microcirculation may be another contributor to futile recanalization. Neutrophils drive microvessel stalls, and RNA/microRNA expression indicative of neutrophil activation is associated with microcirculatory failure. We suggest that collateral failure prior to recanalization and microcirculatory failure after recanalization due to neutrophil stalls are key drivers of futile recanalization.

P2-C-82: *Understanding sensory dysfunction in christianson syndrome*

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Children diagnosed with Christianson Syndrome (CS) have a rare neurodevelopmental disorder caused by a loss-of-function mutation in the SLC9A6 gene encoding the cation/proton exchanger NHE6. This syndrome is characterized by intellectual disability, mutism, autism spectrum disorders, as well as hyposensitivity to pain and aversion to touch. This study aims to identify how changes in NHE6 function result in dysfunctions in sensory perception. We have used a NHE6KO mouse (Mus musculus) model to conduct behavioural tests (von Frey, dynamic brush, radiant heat) to quantify the pain hyposensitivity and aversion to touch in these mice, in comparison to their wildtype (WT) littermates. Using immunohistochemistry (IHC), mice spinal cords will be analyzed for differences in pain and touch fibre connectivity in lamina I-II between the NHE6KO and WT mice. We have also generated a rescuable, tamoxifen dependent NHE6KO mouse model to rescue NHE6 function, and

determine the critical developmental period in which the sensory impairments can be rescued. NHE6KO mice displayed a greater number of nocifensive responses to innocuous mechanical stimuli, from the dynamic brush test, and elevated thermal withdrawal latencies, from the radiant heat test, in comparison to WT mice. Our IHC data will determine if the hypersensitivity to innocuous stimuli is due to the impaired detachment of Aβ fibres from nociceptive circuits in the superficial layers of the dorsal horn. Findings from this project will increase our understanding of the mechanisms of pain tolerance and touch aversion in CS patients.

P2-C-83: *Investigating the Role of Mitochondrial Signaling in the Maintenance of Neuronal Function and Differentiation in the Context of Parkinson's Disease*

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Parkinson's Disease (PD) is characterized by the degeneration of dopaminergic neurons in the Substantia Nigra leading to motor deficits. Overwhelming evidence now suggests that mitochondrial dysfunction is a key feature contributing to the pathology in PD. We have shown that mitochondrial dysfunction can alter the proliferation and differentiation of adult neural stem and progenitor cells, resulting in the dedifferentiation of newborn neurons. Using Opa1 KO as a model for mitochondrial dysfunction, we examined the mitochondrial signaling mechanisms underlying neuronal dedifferentiation. Bulk RNA sequencing was performed in differentiated neurons. We have identified a decrease in the expression of genes involved in neuronal differentiation, including those that regulate neuronal excitability and synapse formation. Using bioinformatic tools, we identified the ATF4 transcription factors as potential regulators of gene expression changes following mitochondrial dysfunction. This evidence led us to hypothesize that mitochondrial dynamics signal in a retrograde manner to the nucleus to repress the expression of genes involved in neuronal differentiation, resulting in impaired neurological function. We will manipulate these key pathways in an effort to restore neuronal function in vitro and in vivo. Elucidating this pathway is key for understanding mechanisms underlying neurodegeneration, and will identify novel therapeutic targets by which to improve neurological function in PD. Supported by a CIHR grant to RSS. University of Ottawa.

P2-C-84: *Investigating cortical reorganization following motor cortex localized photothrombotic stroke in mice using optogenetic motor mapping*

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Background - The current experiment used light-based motor mapping to reveal stroke-induced changes in the representation of forelimb movements within the motor cortex. In contrast to electrode-based motor mapping, optogenetic stimulation allowed us to longitudinally map both hemispheres before and after photothrombotic stroke within the same animals. Methods - Blue light stimulation of the motor cortex through a transcranial window induced forelimb motor movements within the transgenic mouse line, recorded with a high-frame rate camera. Using the recorded movement trajectory from each stimulation site, heat maps were generated to indicate motor sites. Mapping sessions were conducted at baseline and at weekly intervals following a photothrombotic stroke (~1.0mm3) within the motor map. Results - Overall, infarcts targeted to the caudal forelimb area produced a lasting impairment in motor output. Specifically, although movements derived from the injured hemisphere showed partial recovery, the size of the motor representation never reached baseline values exclusively in the contralateral forelimb of stroke induction. Movements derived from the intact hemisphere however returned to baseline values within 2-3 weeks post stroke. Conclusion - Our longitudinal optogenetic motor mapping technique revealed hemisphere- and forelimb- specific changes in movement representation following photothrombotic stroke. Future experiments will investigate the functional role of motor map reorganization through longitudinal behavioural assessment.

P2-C-85: *Investigating the link between adolescent repeated mild traumatic brain injuries and development of autoimmune responses to the CNS*

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Mild traumatic brain injuries (mTBI) represent a major health concern worldwide, with adolescents being particularly prone. Recent studies have highlighted an increased risk of developing multiple sclerosis (MS) in people who had received repeated mTBIs (RmTBIs) earlier in life. However, the cellular and molecular mechanisms underlying this phenomenon are unknown. We have recently developed the lateral impact model of RmTBI that recapitulates the acceleration/deceleration and rotational forces imparted on the brain during mTBI. Using this model, we have shown sex and time-dependent behavioral deficits and neuroinflammatory responses in adolescent mice. We hypothesized such cellular responses following RmTBI could initiate a cascade of events that lead to autoreactive T cell responses. With this in mind, we gave adolescent mice of both sexes RmTBIs or sham injuries. Immediately following the final injury, mice underwent a battery of behavioral tests and then received a diet of 0.2% cuprizone for either 2 or 7-weeks. Cuprizone is a commonly used demyelinating agent, and we hypothesized that mice that had received RmTBIs prior to cuprizone would display a worse behavioral and neuroinflammatory phenotype compared to sham mice. We performed the same

behavioral tasks prior to sacrificing the mice. Upon sacrificing, the spleens were taken for restimulation of splenocytes with myelin. Furthermore, we assessed the extent of gliosis, demyelination, and axonal damage using immunohistochemistry. We expect mice that received RmTBIs during adolescence will display worse behavioral outcomes following cuprizone, and will show increased gliosis, demyelination, and axonal damage. This would provide a possible cellular link between RmTBIs and the development of MS-like disease.

P2-C-86: *The role of extracellular vesicles in Alzheimer's disease: a comparison of methods for the purification and characterization of extracellular vesicles from immortalized cell lines*

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Extracellular vesicles (EVs) are lipid-bound vesicles containing cellular cargo (nucleic acids, lipids, and proteins) which are secreted into the extracellular space and ubiquitous to all cell types. Over the past decade, EVs have been increasingly investigated both for their role in disease and as potential diagnostic biomarkers. EVs have been demonstrated to play a role in the propagation of disease material in Alzheimer's disease (AD) and other neurodegenerative diseases, but the exact mechanism by which this occurs is still unclear. It has been postulated that changes in the autophagic-lysosomal system (A-LS) contribute to the progression of AD, but the relationship between the A-LS and EVs has not yet been elucidated. A major challenge in the investigation of EV-mediated disease pathways is the ability to obtain high yield productions of EVs for analysis. Therefore, purification methods that produce the highest quality yield of EVs are needed. In this study, we compared several commonly used EV purification techniques including ExoQuick plus, sucrose cushion ultracentrifugation, and differential ultracentrifugation, to purify EVs from HEK293 cells expressing tau, C8-D1A astrocytes, and SH-SY5Y cells that have undergone A-LS modulation. The size and yield of the EVs isolated using each purification method was determined by biochemical and biophysical analysis. Overall, the findings from this study allow us to determine the optimal purification method, providing us with the ability to standardize future experiments and maximize EV yield for downstream applications.

P2-C-87: *Investigating extracellular vesicle microRNAs as blood-based biomarkers of neurodegeneration in multiple sclerosis*

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The development of many neurodegenerative disorders begins long before symptom onset, highlighting the need for accessible and quantifiable biomarkers of neuronal damage. In multiple sclerosis (MS), neurodegeneration is the best-known correlate for sustained clinical disability associated with progressive forms of the disease. Currently, there are no biomarkers for disease progression or therapies targeting neurodegeneration in progressive MS. There is an acute need for biomarkers of neuronal damage that may serve as prognostic indicators of disease progression and suggest novel therapeutic targets. MicroRNAs (miRNAs) are small, non-coding RNA molecules that bind and inhibit translation of messenger RNA, making them powerful regulators of gene expression. miRNAs are often packaged into extracellular vesicles (EVs) - small, vesicular bodies derived from the endocytic pathway - which are secreted from cells and abundant in human blood. Here, we use a reductionist in vitro culture system to profile miRNA expression in EVs released from human iPSC-derived neurons challenged with MS-relevant stimuli. We show that iPSC-derived neurons degenerate upon exposure to toxic stimuli and identify a panel of miRNAs that are dysregulated in EVs from degenerating neurons. Expression of candidate miRNAs will be evaluated in neuronal EVs isolated from plasma of MS patients at various stages of disease. We hope to identify a conserved miRNA signature that can be used to monitor neurodegeneration and disease progression in MS, while defining new neuroprotective strategies.

P2-C-88: *Impaired metaplasticity and increased susceptibility to long term depression-like plasticity in the primary motor cortex of focal hand dystonia patients*

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Introduction: Focal hand dystonia (FHD) patients exhibited abnormal long term potentiation (LTP)-like plasticity in the primary motor cortex (M1); however, it is unclear whether depotentiation is also aberrant. Depotentiation can be studied using transcranial magnetic stimulation (TMS) in theta burst stimulation (TBS) mode with intermittent-TBS (iTBS) inducing LTP-like effects followed by continuous-TBS (cTBS) to induce depotentiation. Objective: Investigate whether FHD patients exhibit impaired depotentiation using TBS applied to the M1. Methods: 12 FHD patients and 10 healthy controls were studied in two randomized visits using a potentiation-depotentiation protocol (iTBS[600] and cTBS[150]) and depotentiation-only protocol (iTBS[sham] and cTBS[150]) targeting M1. Motor evoked potential (MEP) amplitudes were measured at baseline ('BL'), immediately after iTBS ('Inter'), 1-minute after cTBS ('T01'), T05, T10, T20, and T30. Results: After the potentiation-depotentiation protocol, unlike healthy controls, FHD patients exhibited a decrease in MEP amplitude ratios to BL ('MEP Ratios') at the Inter timepoint followed by an increase at T20. The depotentiation-only protocol decreased

MEP Ratios in both FHD patients and healthy controls. Conclusion: After the potentiation-depotentiation protocol, FHD patients showed abnormal plasticity regulation. After the depotentiation-only protocol, FHD patients showed increased susceptibility to an LTD-like effect. Thus, impaired metaplasticity and increased susceptibility to LTD-like plasticity could be pathophysiological features of FHD.

P2-C-89: *Synaptic alterations of neuronal outputs from the lateral habenula in the model of chronic social defeat*

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The lateral habenula, the main disappointment center of the brain, has been shown to be hyperactive in depressive disorders. However, how synaptic transmission at its neural outputs is affected in depression is not known. Here, we use optogenetics and electrophysiology to examine synaptic transmission from the LHb to three of its main output targets : the serotoninergic dorsal raphe nucleus (DRN), the rostromedial tegmental nucleus (RMTg), and the ventral tegmental area (VTA), in mice subjected to chronic social defeat stress (CSDS). To selectively activate LHb efferent, an AAV-ChR2-mCherry is first injected in the LHb. Ten days later, mice are subjected to 10 days of CSDS, and tested in the social interaction test to determine their resilience or susceptibility to chronic defeat stress. Acute brain slices are obtained from control, susceptible and resilient mice and synaptic transmission is examined using whole-cell patch clamp recordings. At the LHb-DRN synapses, chronic stress did not change paired-pulse ratio (PPR) but increased the evoked AMPAr/NMDAr ratio in susceptible mice. At the LHb-RMTg synapses, CSDS decreased paired-pulse ratio both in susceptible and resilient mice while decreasing evoked AMPAr/NMDAr ratio in resilient mice. Finally, at the LHb-VTA synapses, CSDS decreased AMPAr/NMDAr ratio in susceptible and resilient mice while no change was observed for PPR. Taken together, these results suggest that LHb neural outputs are differently altered following CSDS, and these synaptic changes may contribute to distinct symptoms found in depressive disorders.

P2-C-90: *A novel femtomolar hemodynamic modulation strategy reveals major microvascular defects in glaucoma at single-pericyte scale*

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Here, we developed a novel live imaging and femto-scale delivery system to study the role of single-pericyte hemodynamics in glaucoma. Ocular hypertension (OHT) was induced by intracameral injection of magnetic microbeads in NG2-DsRed mice, which allow visualization of retinal pericytes. Two-photon laser scanning microscopy (TPLSM) was combined with a femtomolar delivery system (FemtoJet Microinjector) to visualize and modulate single-pericyte longitudinal responses in living mice. Our data show decreased capillary diameter and blood flow at pericyte locations in glaucoma (sham: n=13 capillaries, OHT-2 wks: n=18 capillaries, N=5-7 mice/group, $p<0.01$). Femtomolar delivery of endothelin-1 (ET-1) in glaucomatous mice exacerbated the magnitude and duration of capillary constriction at pericyte locations and decreased blood flow relative to controls (vehicle: n=11 capillaries, ET-1: n=16 capillaries, N=3-5 mice/group, $p<0.001$). In contrast, nitric oxide (NO) donor administration rescued the ability of capillaries to dilate at pericyte locations enhancing blood flow despite OHT (vehicle: n=16 capillaries, NO donor: n=7 capillaries, N=3-5 mice/group, $p<0.01$), suggesting that microvascular defects in glaucoma are reversible. We demonstrate the utility of combining TPLSM live longitudinal imaging and femtomolar delivery of vasoactive substances to study neurovascular defects caused by OHT. Our study identifies pericytes as critical regulators of capillary hemodynamics and unveils their potential as therapeutic targets to restore neurovascular function in glaucoma.

P2-C-91: *Behaviour characterization of the Q175/B6 Huntington's disease mouse model*

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Q175/B6 is a knock-in mouse model of Huntington's disease, a neurodegenerative disorder characterized by loss of motor control and cognitive deficits. The primary site of neurodegeneration in HD is the striatum, a brain region important for motor learning. Studies have found hypoactivity and abnormal rearing in older HD mice during the open field, as well as motor and cognitive deficits on the rotarod and water T-maze tasks at ~10 months of age. This study conducts more detailed behavioural pattern analyses in 2- and 10-month-old male and female Q175 mice during these tasks using the DeepLabCut tracking software and the new Behavioral Segmentation of Open Field in DeepLabCut machine learning program. 10-month-old Q175 mice engaged in less locomotion and sniffing behaviours and more rearing as compared to wild-type in the open field. Both male and female older Q175s showed a greater number of foot slips on the rotarod task. In the water T-maze, 2-month-old Q175 mice took longer than WT to reach the hidden platform during the reversal phase.

However, in the older group, only those that used a striatum-dependent response learning strategy showed a longer latency to reach the platform. These findings reveal that Q175 mice show motor learning and coordination deficits at 10 months of age, as well as reduced exploratory behaviour and potentially increased anxiety-like behaviours in the open field. Younger Q175 mice may show early signs of impairment in cognitive flexibility, and the specific strategy used during motor learning may be more relevant at the older age. Future studies that examine striatal signalling using in vivo fiber photometry during performance of these tasks are needed for evaluation of potential therapeutic treatments in HD. Funded by CIHR Fdn-143210.

P2-C-92: *Bidirectional regulation of glt-1 and glutamate clearance during the progression of a mouse model of Alzheimer's disease*

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Sodium-dependent high affinity glutamate transporters are essential in controlling the spatiotemporal dynamics of glutamate and mitigating toxic effects associated with extracellular glutamate accumulation. Neurodegenerative diseases, in particular Alzheimer disease (AD), are associated with impaired glutamate clearance. Surprisingly, most research into glutamate clearance in AD is conducted once overt symptomology manifests, leaving the contribution of glutamate uptake in the presymptomatic phase largely unexplored. Here, we conducted western blots of GLT-1 (the brain's primary glutamate transporter) and quantified real-time glutamate uptake dynamics in the hippocampus of 1-2-month and 6-month-old 3xTg and age-matched control mice using high-speed imaging of the intensity-based glutamate sensing fluorescent reporter (iGluSnFR) in the hippocampus. At 6-months of age, or when an AD-like phenotype begins to emerge, 3xTg mice exhibited decreased GLT-1 levels and slowed glutamate clearance. Remarkably, at an age-range considered presymptomatic in the AD brain, surface GLT-1 levels were elevated and glutamate was cleared significantly faster in 3xTg mice. Pharmacological manipulation of glutamate transporters suggests that early glutamate clearance acceleration is GLT-1 independent while later slowing is a result of GLT-1 dysfunction. The findings presented suggest glutamate clearance slows with age in the 3xTg model of AD, and that GLT-1 is bidirectionally regulated, with an initial increase in surface GLT-1 levels that decrease once overt AD-like symptomology emerges. Uncovering the mechanism that causes this bidirectional shift in GLT-1 and glutamate clearance as AD progresses could lead to therapeutic treatment strategies for a notoriously hard disease to treat.

P2-C-93: *The effects of pre-tangle pseudophosphorylated human tau on behaviour and synaptic plasticity in the CA1 of the hippocampus*

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Alzheimer's Disease (AD) is characterized by the pathological presence of amyloid beta plaques and tau neurofibrillary tangles in the brain. Available treatments which target amyloid beta or late-stage reversal of AD have proven ineffective at stopping or reversing the progression of the disease. However, therapeutic strategies targeting tau may be a promising alternative. The tau tangle precursor, hyperphosphorylated soluble (pre-tangle) tau can be toxic and appears decades before the onset of clinical symptoms. As such, it is an ideal target for early intervention and this project aims to better understand the role of pre-tangle tau pathology in the progression of AD and to identify features that may aid in early detection and prevention of the disease. Sprague Dawley rats were infused in the CA1 region of the hippocampus 2-3months postnatal with an adeno-associated viral vector containing a pre-tangle pseudophosphorylated human tau (htauE14) gene. At 1-3 & 9-months post-infusion, animals undergo behaviour tests, and changes in synaptic plasticity are assessed. At 1 and 3-month post-infusion, animals who received htauE14 in the CA1 showed significant spatial deficits in comparison to animals who received control infusions. However, there were no trending differences in any of the general or olfactory behaviour tasks. The htauE14 animals also displayed deficits in synaptic plasticity at 1-month post-infusion. These experiments, in parallel, will allow us to better understand pre-clinical stages of AD and could lead to the development of effective treatment strategies.

P2-C-94: *Alteration in spectral activity during wakefulness and slow wave sleep after amyloid-beta oligomer injection in rats*

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Synapse loss and ensuing neuronal death are the best predictors of memory deficits in Alzheimer's disease (AD). Hippocampus-dependent memory for recent facts and events (explicit memory) is the first type of memory that is affected in the disease because of the neurodegenerative process that takes place in the hippocampus of early AD patients. There is mounting evidence from recent studies that soluble low-molecular-weight amyloid-beta oligomers (Aβo), especially oligomers derived from Aβ1-42 peptides, are the most neurotoxic species and correlate extensively with memory deficits in AD patients and animal models. It is also well-established that sleep affects the function of the hippocampus, and that sleep alterations are among the first clinical symptoms observed in AD. The main objective of this project is to determine the impact of soluble Aβo on sleep in a rat model of amyloid pathology. We performed chronic hippocampal injections of soluble Aβ1-42 oligomers in rats and electroencephalographic (EEG) measurements were performed to define wake/sleep alteration.

Time spent in wakefulness, slow-wave sleep (SWS) and paradoxical sleep was preserved in Aβo-injected rats. However, EEG spectral activity measured during wakefulness was increased by Aβo for slow-wave activity (SWA; 0.5-5 Hz) and low-beta activity (16-20 Hz), whereas it was decreased by Aβo during SWS for theta activity (5-9 Hz) and alpha activity (9-12 Hz). Moreover, the theta activity/SWA ratio was decreased during wake and SWS. These differences were significant for the frontal cortex but not for a central recording site. Identifying the specific signature of hippocampal neurodegeneration on sleep features might serve as a non-invasive marker of early AD.

P2-C-95: *Characterization of the interaction between pathological α-synuclein and synaptic cell adhesion molecule neurexins*

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Synucleinopathies are a group of neurodegenerative diseases that imply the misfolding and aggregation of alpha-synuclein (α-syn), an abundant presynaptic protein involved in regulating synaptic vesicles exocytosis. The abnormal aggregation of α-syn within neurons is thought to lead to defects in neuronal functions and ultimately to neuronal death. Additionally, α-syn has been proved to spread between cells in a prion-like manner, thus propagating neurodegeneration throughout the brain. Although the responsible mechanisms for this process remain to be discovered, our screening of synaptic membrane proteins has revealed neurexin (NRX) family members as strong ligands for α-syn. NRXs are important presynaptic adhesion molecules that regulate synaptic properties and transmission. So far, we found that NRXs interact only with aggregated form of α-syn, but not with its monomeric form. Our cell-based and cell-free binding assays both revealed a dissociation constant in the nanomolar range (~500nM). Finally, we showed that α-syn specifically interacts with the β-isoforms of NRXs (NRXβ) through their unique histidine rich domain. Given our preliminary data, we hypothesized that NRXs participate in the trans-synaptic propagation of α-syn through their direct interaction. We are currently assessing whether and how NRXβ mediate α-syn internalization and propagation in vitro using biotin surface labelling and colocalization experiments as well as the monitoring of the phosphorylated α-syn accumulation in neuron culture.

P2-C-96: *The impact of inflammation and general anesthesia on memory and executive function in mice*

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Introduction: Persistent cognitive deficits can occur in a subset of patients after surgery. Inflammation and exposure to general anesthetic drugs are thought to contribute to the development of these deficits; however, the relative impact of these factors remains poorly understood. The goal of this study was to compare the relative impact of inflammation, general anesthesia, and their combination on memory and executive function. Methods: Mice were treated with lipopolysaccharide (LPS) or vehicle to induce inflammation, and one day later were treated with the general anesthetic etomidate or vehicle. Levels of proinflammatory cytokines and markers of glial activation were measured in the hippocampus 24 and 72 h after LPS. Starting 24 h after anesthesia, recognition memory and executive function were assessed using novel object recognition and puzzle box assays, respectively. Results and conclusions: LPS induced neuroinflammation up to 72 h after injection, as indicated by increased levels of proinflammatory cytokines and microglial activation. Recognition memory was impaired in mice treated with LPS alone or co-treated with LPS and etomidate, but not with etomidate alone, indicating that memory deficits were driven by inflammation. Interestingly, executive function was only impaired in mice treated with the combination of LPS and etomidate, suggesting that the general anesthetic etomidate may unmask latent deficits induced by inflammation. Thus, an interplay between inflammation and general anesthesia may be critical in the development of cognitive deficits after surgery.

P2-C-97: *Age-dependent changes of the morphofunctional integrity of the human neuromuscular junction.*

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Several changes occur in normal aging contributing to a loss of skeletal muscle mass and function. A key factor contributing to muscle changes is the alterations of neuromuscular junctions (NMJ). NMJs are tripartite synapses composed of a presynaptic nerve terminal, postsynaptic fiber and perisynaptic Schwann cells (PSCs). However, the human NMJ remains largely understudied. We used an adapted needle biopsy method to study the morphofunctional alterations in aging. The cohort was composed of 4 young (18-30 years) and 5 older adults (over 55 years). Several physiological measurements (physical activity level, muscle strength, etc.) were assessed prior to the biopsy. Biopsy samples were stained by immunohistochemistry for the nerve terminal (NFM/SV2), postsynaptic nAChRs (α-btx), PSCs (s100β) and fiber type (MHC I) and imaged using confocal microscopy. NMJs were characterised for each of their components and compared between age groups. Human NMJs have a very distinct organisation compared to rodent NMJs, especially regarding postsynaptic and PSCs morphology. Comparative analyses revealed that the NMJ structure remained relatively stable in aging. However, larger number of denervated NMJs and lower glial coverage were observed in older individuals. These

data will be correlated with the participants' physiological data to identify which NMJ parameters better reflect the physiological state of each individual. Our results will provide a better understanding of neuromuscular aging and develop better therapeutic approaches to limit muscle weakening in aging.

2D. Sensory and Motor Systems

P2-D-98: *Slow touch: Can the observation of slower movements enhance tactile processing?*

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Movement, and the mere observation of movement, can alter our perception of sensory events. Indeed, humans can exhibit reduced tactile perception during movement (Juravle et al., 2016) or when simply observing a reach as compared to a static grasp (Vastano et al., 2016). Further, tactile processing during movement may depend on movement speed (i.e., reduced perception only when moving beyond a critical speed: Cybulska-Klosowicz et al., 2011). However, the relationship between observed movement speed and tactile processing is not known. Accordingly, participants observed videos of a model performing reaching and grasping movements at three different movement speeds. To assess tactile processing, weak electrical stimuli of different amplitudes were presented to participants' right thumb when the model was at their starting position (i.e., 500 ms before movement onset) or when the model's limb reached peak velocity (PV). Perceptual thresholds were then calculated for the pre-movement stimulation time and for each observed movement speed. When observing slow movements (i.e., PV: 155 mm/second), participants' perceptual thresholds were significantly lower than for the pre-movement stimulation time, which did not differ from the threshold when observing movements with medium (PV: 547 mm/s) or fast peak limb velocities (i.e., PV: 995 mm/s). Thus, as compared to pre-movement states, tactile perception during action observation can depend on the observed movement speed. More importantly, our data provides evidence for tactile facilitation when observing slower reaching movements.

P2-D-99: *Why we fall: Probing the cerebellar contribution to aging using chemogenetics*

Eviatar Fields[1], Andy Huang[1], Megan Kern[1], Alanna Watt[1]

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Declines in motor coordination are common in aging and limit a person's quality of life. The cerebellum is critically involved in motor coordination. Cerebellar Purkinje cells fire spontaneous action potentials at high frequencies, which is disrupted in several animal models of ataxia. Rescuing Purkinje cell firing rate deficits in mouse models of ataxia has been shown to improve motor coordination, suggesting that high frequency firing of Purkinje cells is important for normal cerebellar function. We wondered whether cerebellar alterations contribute to aging-related motor decline. To address this, we measured motor coordination in healthy C57Bl/6J mice across their adult lifespan, from young to old adult, and observed a progressive age-related decline. We then performed loose cell-attached recordings from Purkinje cells to measure spontaneous action potential firing in acute cerebellar slices. We observed an age-dependent reduction in Purkinje cell firing rates, suggesting that Purkinje cell firing might contribute to the decline in motor coordination we observed. To determine whether Purkinje cell firing alterations directly contribute to motor dysfunction in aging, we used viral delivery of chemogenetic receptors to modulate Purkinje cell action potential activity. We found that chemogenetically reducing Purkinje cell firing rates led to a decrease in motor coordination in young mice, suggesting that Purkinje cell firing output directly modulates motor coordination. Our data suggest that aging-related Purkinje cell firing deficits contribute to declining motor coordination observed in aging individuals.

P2-D-100: *Sympathetic preganglionic innervation from locomotor-related lumbar V3 spinal neurons*

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In Canada, ~80000 people live with spinal cord injury (SCI). Dysregulation of sympathetic function is common after SCI as connections between autonomic centers in the brainstem are severed from spinal sympathetic preganglionic neurons (SPNs) that regulate sympathetic outflow. However, SPNs located in intermediate lamina (IML) of T1-L2 spinal cord (SC) remain active, and lumbar electrical stimulation increases thoracic (T) sympathetic output and improves cardiovascular function after cervical SCI. The source of this excitatory neuronal input to SPNs is unknown. We believe ascending propriospinal interneurons (INs) located in lumbar (L) SC synapsing on T-SPNs are involved. Thus, innervation patterns from L-V3 INs on T-IML SPNs were investigated in Sim1CreTdTom mice. Of all excitatory input apposed to T-SPNs, ~20% arose from V3 INs projections (TdTom+/VGlut2+, n=3). To determine if L-V3 INs show distinct distribution patterns, BDA was injected into either L2 or L4/5. L2 injections resulted in 2x more V3 contacts in rostral (T1-6) vs. caudal (T6-T12) segments. Whereas L4/5 injections resulted in 2.6x more contacts in caudal segments (BDA+/TdTom+). Injections of CTB targeting T8 IML revealed that over half of V3 INs in L1-6 provided input to this region, with a slightly higher contribution from contralateral V3 INs (65% of V3D; 55% V3V ipsi- vs. ~70% contralateral, n=2). This is the first demonstration that lumbar V3 INs provide direct excitatory synaptic input onto T SPNs

(~20%) and suggest that locomotor-related lumbar V3 INs may activate sympathetic output during movement.

P2-D-101: *Functionally Distinct NPAS4-Expressing Somatostatin Interneuron Ensembles Critical for Motor Skill Learning*

Jungwoo Yang[1], Pablo Serrano[1], Xuming Yin[1], Xiaochen Sun[2], Yingxi Lin[2], Simon Chen[1]

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Local GABAergic inhibitory neurons are known to play an essential role in memory formation and allocation by modulating level of inhibition to downstream excitatory neuronal ensembles. During motor learning, dendritic spines on pyramidal neurons (PN) undergo reorganization in motor cortex (M1), which coincides with subtype-specific axonal bouton changes in somatostatin-expressing inhibitory neurons (SOM-IN) and parvalbumin-expressing inhibitory neurons (PV-IN). Moreover, SOM-IN-mediated inhibition has been shown to regulate spine reorganization on PN. However, the molecular mechanisms that underlie changes in inhibition, and whether the changes arise from all SOM-IN remain unclear. Here, we identified that NPAS4, transcription factor, is selectively expressed in SOM-IN, but not in PV-IN or PN, during motor learning in M1. Combining in vivo two-photon imaging with a head-fixed pellet reaching task, we found that activity was reduced among NPAS4-expressing SOM-IN during task-related movements compared to non-NPAS4-expressing SOM-IN. Region- and cell-type specific deletion of Npas4 within SOM-IN in M1 disrupted the spine elimination process and impaired motor skill acquisition. Chemogenetic activation of NPAS4-expressing ensembles was sufficient to impair motor learning and alter the spine elimination process. Together, our results reveal an instructive role of NPAS4 within the microcircuits, in which it modulates the inhibition of a distinct subset of SOM-IN during motor learning to promote spine stabilization of downstream PN that are important for motor skill acquisition.

P2-D-102: *Cerebellar influence on motor cortical inhibitory control during motor adaptation*

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Motor adaptation is marked by neurophysiological changes in the motor cortex; however, other regions of the motor network (i.e cerebellum and premotor cortex) also contribute to this process. Enhancing cerebellar activity has been shown to increase the rate of motor adaptation, though it is unclear what mechanisms of adaptation are influenced by the cerebellum. Pre-movement beta event-related desynchronization (ERD), which reflects a release of synchronized inhibitory control in the

premotor cortex during movement planning, is one mechanism that could be modulated by the cerebellum. We hypothesized that enhancing cerebellar activity with intermittent theta burst stimulation (iTBS) would improve participants' learning rate and modulate beta power changes during motor adaptation. Participants received either active or sham cerebellar iTBS 10 minutes prior to completing motor training on a visuomotor rotation task. The magnitude of the beta ERD was obtained by measuring the beta power change between the rest and movement preparation phase of each trial. Preliminary results show a greater learning rate in the active iTBS group. The active iTBS group also showed a greater change in beta ERD during adaptation, measured in the initial 2-minute block of training. This difference in magnitude of beta ERD between groups is indicative of a cerebellar modulation of the motor cortical inhibitory control network. Results from this study will further understanding of the connections between the cerebellum and motor cortex and inform future skill training and rehabilitation protocols.

P2-D-103: *Functional specific corticofugal connectivity promotes the plasticity of optokinetic reflex*

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The visual cortex sends massive corticofugal projection to the brainstem, by which the cortex can modulate the brainstem-driven innate behaviors. One example is the optokinetic reflex (OKR), an involuntary eye movement to stabilize retinal images. A recent study showed that the corticofugal projection enabled the visual cortex to potentiate OKR to make up the loss of other ocular behaviors. Despite its importance, the underlying mechanisms remain unclear. We used an interdisciplinary approach to explore the substrate of this cortical function. Anatomically, we found that corticofugal neurons innervating the brainstem OKR circuit primarily came from anterior V1 and posterior higher visual areas, and synapsed on one brainstem population. Moreover, behavioral tests showed that above cortical areas and brainstem population were required for the cortical modulation of OKR. Next, with calcium imaging, we discovered that those corticofugal neurons shared similar functional properties to their postsynaptic target in the brainstem. Interestingly, following OKR potentiation cortical activity evoked by temporal-nasal motion was boosted only in the neurons preferring temporal-nasal direction. Finally, modeling showed that the direction specific connectivity and activity potentiation of corticofugal neurons provided an efficient way to supply extra cortical innervation in support of OKR potentiation. Altogether, our results suggest that the corticofugal projection and its brainstem partner form a distinct pathway through which the visual cortex sends functional relevant information to the brainstem.

P2-D-104: *In vivo characterization of cortical noradrenergic activity during motor learning using an optical noradrenaline sensor in a mouse model of autism*

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Clinical studies have reported that children with autism spectrum disorder (ASD) often exhibit difficulties with the acquisition of new motor movements; these motor symptoms can present earlier than social or cognitive indicators, but underlying mechanisms responsible for these motor learning disruptions remain unclear. Noradrenaline (NA) exerts powerful control over neuronal activity, and contemporary perspectives highlight the abundance of ASD symptoms that can be viewed through a lens of inefficient neuromodulation by the locus coeruleus (LC) system. Recent work in our lab revealed dysregulation in LC-NA function as a culprit of motor learning delays. Using the 16p11.2 deletion mouse model (+/-) of ASD, we found that these mice exhibit delayed motor learning caused by a reduction of NA levels in primary motor cortex (M1). Since it is well established that NA regulates proper motor execution in M1, we sought next to fully characterize NA levels during learning. Thus, I employed a recently developed optical NA sensor, combined with in vivo 2 photon imaging, to visualize spatiotemporal release patterns of NA in M1. I found M1 NA levels are elevated during running in wild type mice, and become more reliable with learning. In contrast, 16p11.2+/- mice display an increase of M1 NA levels in later learning stages, with no change in reliability. These results align with our previous work, confirming a crucial role for LC NA in motor learning. This study provides a novel glimpse into the LC NA system in ASD, which can provide valuable insight for clinicians.

P2-D-105: *Optogenetic modulation of the hedonic value associated with gentle touch*

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Gentle touch is a unique sensory modality capable of evoking strong negative and positive emotions depending on factors such as environmental and physiological states. Sensory neurons expressing MrgprB4 detect gentle stroking in mice and their activation is known to be positively reinforcing. This project uses optogenetics and behavioral techniques to assess whether activation of channelrhodopsin (ChR2) expressing MrgprB4+ afferents signal positively valenced tactile information and whether this emotional valence can be bidirectionally modified through various interventions. To activate primary afferents, we used a spinal implant in male mice expressing ChR2 in MrgprB4+ afferents. The implant did not produce any motor or sensory deficits and could be used to deliver blue light to the central terminals of the primary afferents. In a real-time place preference assay these mice preferred to spend more time in the blue light paired arm during stimulation compared to their

baseline preference. We also found that mice suffering from a nerve injury did not show this preference indicating that the positively reinforcing nature of this stimulation is plastic and diminished in chronic pain. To elucidate the downstream circuits recruited in response to stimulation, in our nerve injured and sham animals, we are also performing c-fos staining and analysis in the spinal cord and brain. Furthermore, to assess whether this plasticity is bidirectional, we also attempted to augment the blue light preference through administration of oxytocin in naïve implanted mice, though our results failed to reveal an oxytocin mediated augmentation of place preference. Future experiments will include the use of female mice and administration of other known compounds with touch enhancing properties.

P2-D-106: *Non-random motifs underlie cerebellar information transfer between Purkinje cells and neurons of the cerebellar nuclei*

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Circuits in the brain are built from the connections between neurons, and the spatial properties of these connections influence circuit function. In the cerebellum, Purkinje cells integrate extensive synaptic input and transmit this information to cerebellar nuclei neurons which communicate with the rest of the brain. The connections between Purkinje cells and cerebellar nuclei neurons represent a crucial component of cerebellar information processing, but how Purkinje cells converge onto cerebellar nuclei neurons is poorly understood. To identify the spatial properties of Purkinje cell-cerebellar nuclei connections, we performed whole-cell patch-clamp recordings from fastigial cerebellar nuclei neurons in acute slices from mice expressing ChR2 in Purkinje cells. We focally stimulated Purkinje cell axons with blue light in multiple locations to produce spatial connectivity maps revealing patterns of Purkinje cell convergence onto cerebellar nuclei neurons. From these maps, we analyzed convergence "motifs," or non-random spatial patterns, at the functional and spatial levels of cerebellar transverse zones. We found that a subset of cerebellar nuclei neurons receives most input from a single zone, but these cells were less numerous than predicted by a random model. We also found that a subset of cerebellar nuclei neurons receive input from multiple zones, and that this multi-zonal input motif was observed more frequently than predicted. This non-random connectivity suggests that cerebellar nuclei neurons integrate information from functionally distinct Purkinje cells.

P2-D-107: *Hyperactivity of the pontine reticular nucleus underlies increased acoustic startle in female, but not male, Cntnap2 knock-out rats*

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The contactin-associated protein-like 2 (CNTNAP2) gene encodes for the CASPR2 protein, which plays an essential role in neurodevelopment. Mutations in CNTNAP2 are associated with various neurodevelopmental disorders, including autism spectrum disorder and schizophrenia. Rats with loss of function of Cntnap2 (Cntnap2-/-) show increased acoustic startle response (ASR) and decreased sensorimotor gating, measured through prepulse inhibition (PPI). The neural basis of this altered auditory processing in Cntnap2-/- rats is currently unknown. We used in vivo extracellular electrophysiology to record from brainstem structures that mediate ASR and PPI, which are the pontine reticular nucleus (PnC) and pedunculopontine tegmental nucleus (PPTg), respectively. Female Cntnap2-/- rats showed increased PnC firing rates compared to female wildtypes, whereas there were no genotypic differences in male rats, even though both female and male Cntnap2-/- rats show increased ASR. In contrast, we found no genotypic differences in PPTg activity in either females or males, as well as no genotypic differences in the inhibition of PnC firing rates, indicating that alterations in the firing rates of these brainstem structures are not responsible for decreased PPI in Cntnap2-/- rats. We conclude that the auditory processing changes seen in Cntnap2-/- rats are associated with, but cannot be fully explained by, differences in PnC activity. Furthermore, the loss of function of Cntnap2 has differential effects in female and male rats.

P2-D-108: *Electroconvulsive seizures alleviate motor deficits and neuropathology in Parkinson's disease: Evidence from in vivo and in vitro models*

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Parkinson's disease (PD) is characterized by the formation of toxic, fibrillar form alpha-synuclein (α-Syn) protein aggregates in dopaminergic neurons. This leads to degeneration of the substantia nigra pars compacta (SNc) and its targets, causing the associated motor function deficits, including tremor, rigidity and bradykinesia. While seizures are an uncommon comorbidity in PD, in those who experience a seizure, it temporarily but significantly relieves their motor symptoms. This suggests that there is potential opposing interaction between these two disorders involving the modulation of neuronal activity, however the mechanism is unknown. Here, we hypothesize that early modulation of neuronal activity will prevent PD progression. First, using an in vitro model of PD, we found that elevation of neuronal membrane potential by increased extracellular potassium concentration, blocking inhibitory GABAA receptors or direct current stimulation (DCS) significantly reduced the intracellular accumulation of α-Syn fibrils. Next, using a well-established in vivo model of PD, we found

that electroconvulsive seizures (ECS) early in disease progression results in a significant improvement of motor deficits. These results strongly support that seizures can alleviate motor deficits in PD through regulating α-Syn aggregation, and will help gain a better understanding of how to use neuromodulation as a treatment option for PD patients.

P2-D-109: *Altered tactile sensation in mouse models of neurodevelopmental GRIN disorder*

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The N-methyl-D-aspartate receptor (NMDAR) has been widely studied for its role in learning and memory. However, the role of NMDAR in somatosensory functions is less well characterized and could explain GRIN disorder, caused by pathogenic mutations in GRIN genes. We assessed mechano- and thermo-sensation in mouse models of GRIN disorder that carry either a knockdown mutation (Grin1-/-) or a patient variant (Grin1+/Q536R) reducing binding of glycine to the GluN1 subunit. Grin1-/- mice showed changes in texture preference, delayed removal of an adhesive object placed on the snout, increased immobility induced by pinching their scruff and increased threshold to mechanical pain assessed using the von Frey test. These findings suggest the reduced mechanosensory function in Grin1-/- mice. Grin1+/- mice show intermediate phenotypes of these measures. In contrast to mechanosensation, Grin1-/- and Grin1+/- mice exhibited increased sensitivity to heat in a gene-dose dependent manner. Surprisingly, Grin1+/Q536R mice exhibited opposite mechano- and thermal-sensation phenotypes in comparison with Grin1-/- mice. The GluN1 subunit is known to interact with the temperature-sensing channels TRPA1 and TRPV1, and we hypothesize that GluN1 deficiency enhances TRP channel activation. To probe these relationships further, we will conduct biochemical, histological, and immunohistochemical analyses of mouse paws and dorsal root ganglia. We will also employ RNA sequencing of dorsal root ganglion tissue. NMDARs may play a critical role in peripheral somatosensation, suggesting that PNS-restricted drugs may ameliorate some symptoms of GRIN disorder.

P2-D-110: *Altered subpopulations of mechano-sensitive primary afferents in response to peripheral nerve injury*

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The underlying mechanism of mechanical allodynia, the major and most debilitating symptom of neuropathic pain, remains elusive. There is ongoing debate regarding whether a lowering of the

threshold of peripheral nociceptors underlies allodynia. To answer this question, we quantified the mechanical responses of populations of nociceptors from both nerve-injured and sham-control mice. We performed in vivo calcium imaging on lumbar DRGs from anesthetized NaV1.8-GCaMP6s mice, in which most nociceptors were labelled with the genetically-encoded calcium indicator, GCaMP6s. A series of indentation stimuli, of varying pressure, were applied to the hind paw using a feedback-controlled mechanical stimulator. Our results showed that, as a population, the activity level of nociceptors encode the intensity of mechanical stimulation in a graded fashion. The median activation threshold of the overall population of NaV1.8 neurons appeared lower in nerve injured mice compared to control mice. We found however that the distribution of thresholds reflected two subpopulations. Following nerve injury, the higher threshold subpopulation disappeared, explaining the apparent overall threshold decrease. Yet, the median threshold of the lower threshold subpopulation did not change. Thus, our results show that lowering of the activation threshold of nociceptors cannot explain the mechanical hypersensitivity in response to nerve injury. The loss of the high threshold subpopulation after nerve injured is intriguing and may have functional impacts in central processing that remain to be explored.

P2-D-111: *Investigating the role of long-range projecting VIP-expressing neurons of the Facial Motor Nucleus*

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Most vertebrates such as rodents utilize the vestibular system to maintain their postural equilibrium and balance. The medial vestibular nuclei (MVN) is a key hub in integrating the vestibular sensory inputs; however, how different regions that input to MVN are involved in regulating the postural equilibrium and balance remains to be elucidated. By screening through the VIP-Cre::Ai9 mouse line, we identified a population of vasoactive intestinal peptide (VIP)-expressing neurons in the facial motor nucleus (FMN) of the brainstem that send long-range projections to MVN. While the lower motor neurons in FMN mediate specific orofacial and vibrissal muscle activities, it is unclear of the roles of the MVN-projecting FMN VIP-expressing neurons. Here, we combined behavioral, ablation, and viral tracing methods to dissect how FMN-VIP neurons contribute to the vestibular activity. Our results showed that the majority of FMN-VIP neurons are GABAergic. Ablating FMN-VIP neurons by expressing taCasp3-TEVp altered the animals' descending kinematics during a vertical pole test. Interestingly, animals with MVN neuronal ablation displayed a similar abnormal descending kinematic phenotype. We further discovered that the FMN-VIP ablated animals also show lower ability in postural maintenance and higher variations in their balance response trajectory in the horizontal beam task (HBT), indicating a role of FMN-VIP neurons in vestibular function. Altogether, our results reveal a

previously unknown connection between FMN and MVN and provide direct evidence on the role of FMN in regulating vestibular activity.

P2-D-112: *Handedness effects on imagery of fine motor movements: an electroencephalographic investigation*

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The mu rhythm (8-12 Hz) is an oscillatory brain activity recorded over the human motor regions that is reliably suppressed during both imagined and physical movements. It is increasingly theorized that the pattern of this suppression during imagined movements varies according to hand dominance. However, most of this research has focused on imagery of gross motor movements. A comprehensive understanding of how hand dominance affects motor imagery is required if the process' potential clinical applications are to be optimized. We recorded continuous EEG activity while 38 participants (18 left hand dominant, 20 right hand dominant) completed an objective motor imagery task of fine motor movements. Patterns of mu suppression significantly diverged between the two groups during imagery of movements that involved the right hand. In particular, left-handed participants exhibited greater mu suppression over motor regions during correct responses to right hand questions, whereas right-handed participants did not exhibit this effect. No such divergence between two groups was found during left hand questions. These results suggest that while left-handed participants exerted greater effort to imagine movements accurately with their non-dominant hand, right-handed participants did not. Hand dominance thus appears to result in differential patterns of neural activity during the imagination of fine motor movements in left-handed versus right-handed individuals. Clinical applications of motor imagery will thus benefit from taking the hand dominance of individuals into consideration

P2-D-113: *Learning of a mirror reversal and its generalization provides distinguishing mechanisms between de novo learning and motor adaptation*

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When people encounter movement errors, they process these errors to correct for subsequent movements. Such error processing contributes to adapting well-known movements and acquiring new motor skills (de novo learning). Previous studies have compared these two types of motor

learning, however, several aspects of de novo learning, including its retention and generalization, still warrant investigation. Here, participants completed an online version of the mirror reversal task, a paradigm that captures de novo learning mechanisms, across two sessions. In session 1 (N = 63), participants reached to three targets located in the upper-right quadrant of the workspace (5, 45, 85 degrees in polar coordinates), with the mirror located along the vertical midline axis. Although targets farther from the mirror axis produced larger errors, we found that asymptotic learning did not differ across target locations. Moreover, we observed quick progression in learning and no aftereffects. Participants returned for a second session (N = 48; days apart: M = 4.77, SD = 2.52), and showed retention of learning upon re-experiencing the perturbation. They then reached for corresponding target locations within the lower-right and upper-left quadrants of the workspace, followed by reaches using their opposite and untrained hand. We observed almost complete and near immediate generalization of learning to targets across the workspace and the opposite hand. These results provide further behavioral mechanisms that distinguish de novo learning from adaptation.

P2-D-114: *Analysis of social behaviors in mice with altered accessory olfactory bulb wiring*

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The accessory olfactory system controls social and sexual interactions in mice that are critical for their survival. Vomeronasal sensory neurons (VSNs) form synapses with dendrites of second order neurons in homogenously innervated glomeruli of the accessory olfactory bulb (AOB). Proper organization of the AOB circuitry ensures that phenotypic qualities of chemosignals detected by VSNs are represented into maps of glomerular activation. The accurate coalescence of VSN axons into glomeruli requires expression of members of the Kirrel family of cell adhesion proteins on these axons. We have shown that either ablating expression of Kirrel3 (Kirrel3-/-), or specifically inhibiting Kirrel3 homophilic adhesion properties (Kirrel3Q128A/Q128A), in mice leads to a disorganization of the glomerular layer in the AOB. Here, we assess the performance of these two mouse models in behavioural assays involving social interactions. We find that Kirrel3-/- and Kirrel3Q128A/Q128A male mice display no change in a social preference test but have reduced male-male aggression. While Kirrel3-/- and Kirrel3Q128A/Q128A male mice showed no difference in a male-female urine preference test, urine dilution tests revealed increased detection thresholds to both male and female urine in these mice. In contrast, sensitivity to an attractive or aversive odorant was unchanged in both models. Taken together, our results indicate that the reduced male-male aggression we observe in two separate Kirrel3 loss-of-function mouse models is associated with decreased sensitivity to male urine chemosignals.

2E. Homeostatic and Neuroendocrine Systems

P2-E-115: *Role of Adipose Triglyceride Lipase (ATGL) in neuronal lipolysis and control of energy balance by melanocortin neurons.*

Danie Majeur[1], Romane Manceau[1], Khalil Bouyakdan[2], Demetra Rodaros[2], Marie-Flore Fourn[1], Stephanie Fulton[3], Thierry Alquier[4]

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Melanocortin neurons of the arcuate hypothalamus (ARC) integrate metabolic signals to regulate energy balance. Evidence suggests this mechanism involves fatty acids (FA) released from intracellular triglycerides (TG) stored in lipid droplets (LD). This is supported by our data showing that neurons accumulate exogenous FA into TG and that neuronal ARC knockdown of Adipose Triglyceride Lipase (ATGL), the first lipase hydrolysing LD, modulates energy homeostasis in mice. However, regulation of LD by ATGL in ARC neurons and its role in the control of energy balance by melanocortin neurons remain unknown. Our lipidomics data show that neuronal LD are enriched with palmitate and oleate. Esterified FA levels are increased by ATGL inhibition (ATGLi) in cultured ARC neurons. Our imaging results show that neurons accumulate LD in response to oleate and ATGLi. ATGLi reduces neuronal LD lipolysis and decreases forskolin-induced LD lipolysis. Insulin and norepinephrine do not affect LD. FA released upon ATGL activation are in part oxidized in the mitochondria. In primary melanocortin neurons, oleate stimulates LD formation. ATGL KO in mouse melanocortin neurons (Cre-Lox) does not affect parameters of energy balance in fasted or fed states, metabolic responses to stress nor susceptibility to obesity in both sexes. Animals will be exposed to cold to assess thermoregulation. Our data shows that ATGL regulates lipolysis and LD dynamics in ARC neurons in vitro but suggests that ATGL is not involved in the control of energy balance by melanocortin neurons. Funding: CIHR, NSERC, FRQS

P2-E-116: *Hypothalamic expression of threat and precaution*

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When faced with uncertainty, organisms take precautionary measures that guard against low probability, high impact events that may have grave consequences. The release of glucocorticoids is a well-studied hallmark of such measures, yet how precaution is represented in the brain is poorly

understood. Corticotropin-releasing hormone neurons of the paraventricular nucleus of the hypothalamus (CRHPVN) control glucocorticoid levels. Here we performed in vivo imaging in freely behaving mice and show that uncertainty increases the activity of the majority of CRHPVN neurons. These are not novelty responses as repeated exposure to the same context elicits a similar response. Furthermore, the relative increase in activity of individual cells is preserved from one day to the next. If these responses are precautionary, then a high impact, aversive event should increase precaution in the future. Consistent with this hypothesis, footshock increases the response of CRHPVN neurons to that context on the next day. Individual cells maintain a faithful representation of this heightened precautionary state over multiple days. This increase is due to a greater contribution from cells that had a low activity profile to uncertainty but show high footshock sensitivity. These findings delineate an entrenched precautionary representation in CRHPVN neurons that is scaled by aversive experience. An inappropriate precautionary response to environmental cues may contribute to the emergence of neuropsychiatric stress disorders.

P2-E-117: *Hippocampal microstructural abnormality in obesity*

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Objective: Obesity induces a state of chronic low-grade neuroinflammation. Neuroinflammation may lead to abnormal diffusivity in structures highly susceptible to chronic physiologic stress, including the hippocampus. This study aims to investigate the association between body mass index (BMI) and DTI-derived diffusivity metrics in hippocampal subregions. Methods: 3T T1 and DWI MRI scans from 455 health controls were selected from the HCP database. FreeSurfer v7.2 was utilized to segment the hippocampus into Cornu Ammonis (CA1-CA4), subiculum, head, body and tail, and transform these segmentations into DWI space. Fractional anisotropy (FA), axonal, radial and mean diffusivities (AD, RD, MD) were extracted from all segmentations via FSL v6.0.1. Spearman's correlation and Mann Whitney U-test were utilized for associations and group difference analyses. Results: 455 subjects (181M, 274F, age = mean ± SD, 28.7 ± 3.7), were included in this study. Bilateral whole hippocampal AD, RD and MD values were significantly negatively correlated with BMI ($p<0.001$). Subfield analysis revealed significant negative correlations between AD, RD and MD in CA1-4, subiculum, head, body and tail and BMI (all corrected $p<0.05$). Group level analysis between subjects with BMI <25 vs. BMI ≥ 25, revealed significantly reduced AD, RD and MD values in all subregions in the lower BMI group (all corrected $p<0.05$). Conclusion: Our study reports the impact of obesity on hippocampal subregion microstructure in a young cohort. These results implicate potential early neuroinflammation in the hippocampus.

P2-E-118: *Microglial Adipose Triglyceride Lipase (ATGL) regulates neuroinflammation and diet-induced obesity in rodents*

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Pro-inflammatory microglia contribute to dysregulation of energy and glucose homeostasis. Lipid droplets (LD) act as intracellular triglyceride (TG) stores and accumulate within microglia during pro-inflammatory conditions. Diet-induced obesity (DIO) triggers microglial neuroinflammatory responses. Adipose triglyceride lipase (ATGL) catalyzes TG hydrolysis in LD. Loss of ATGL reduces inflammation in macrophages, suggesting an active role for LD lipolysis in inflammatory signaling pathways. We thus hypothesize that microglial ATGL negatively regulates neuroinflammation in response to inflammation and alters the behavioral and metabolic responses to a high fat diet. Inhibition of ATGL activity in vitro and in vivo reduced expression of pro-inflammatory cytokines in response to lipopolysaccharide (LPS). The knock-out (KO) of ATGL specifically in microglia of adult mice (inducible Cre-Lox strategy) did not affect parameters of energy balance in chow-fed male or female mice. However, loss of ATGL increased susceptibility to DIO without affecting food intake, and improved glucose tolerance independently from circulating insulin levels. A potential protection to LPS-induced anxio-depressive behaviors was also observed in this model. Together these data suggest that microglial ATGL inhibition or deficiency reduces neuroinflammation and may have a beneficial impact on glucoregulatory responses. Funded by CIHR & CardioMetabolic health, Diabetes and Obesity FRQS network

P2-E-119: *Effects of maternal high fat diet on microglia activation in offspring*

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Maternal consumption of a high saturated-fat diet (mHFD) is linked to disruptions in the physiological response to stress in offspring. The main mediator of the neuroendocrine stress response is the hypothalamic-pituitary-adrenal (HPA) axis, which is sensitive to mHFD exposure. The hippocampus and amygdala, refine the response to stress by modulating expression of HPA axis related genes. These changes in gene expression often present in sex-specific ways because the HPA axis is more vulnerable to early life stressors and has increased reactivity in females. Additionally, mHFD exposure is sensed by microglia, which in turn disrupt the HPA axis through activation of the inflammatory

response. Prior studies have focused on adult offspring exposed to mHFD, but there remains a gap in knowledge about the early life programming of microglia, which undergo morphological and functional changes in response to stressors. PND 7 corresponds to a critical period in which rats are hyporesponsive to stress. We hypothesized mHFD would alter the immunophenotype of offspring to become primed for inflammation. In this study, female Long Evans rats were fed HFD or control diet 4 weeks prior to mating, during gestation and lactation. Brain tissue from the hippocampus and amygdala of PND7 offspring were collected for qPCR and immunohistochemistry analysis. Results showed diet effects and sex effects on the immunophenotypes of microglia, suggesting microglia were more activated with mHFD exposure. Ultimately, this study provides mechanistic insight into microglia activation by exposure to mHFD.

P2-E-120: *The modulation of subfornical organ neurons, in situ, by neurotensin*

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Neurotensin (NT) is a 13 amino-acid peptide which is both a hormone and neuromodulator. Through it's 3-4 known receptors, NT is shown to influence several physiological responses including autonomic output, hydromineral balance, and cardiovascular regulation. Recent transcriptomic studies have revealed that the subfornical organ (SFO) expresses a high abundance of neurotensin receptors (NTSR), specifically NTSR2 and NTSR3, with levels comparable to other prominent neuromodulators that act in this region. The SFO is known for its involvement in cardiovascular regulation, sympathetic output, and hydromineral balance. As a circumventricular organ, it lacks the blood brain barrier, providing a direct interface with peptides in circulation, in addition to centrally released signals in cerebrospinal fluid. Both NT and the SFO have been found to influence satiety and water intake; thus, the SFO, through various peptides, and NT as a peptide have both been found to play an important role in hydromineral balance; which, in turn, plays a role in cardiovascular regulation. Due to their intersecting areas of influence, and as the SFO is a major integration center for peripheral and central signals, it is hypothesized that this neuropeptide modulates neurons in this region to elicit physiological responses. Voltage clamp recordings of coronal SFO slices demonstrate that NT (1μM) modulates synaptic activity in 60% of SFO neurons tested, in situ. Further experiments are aimed at determining distribution among subpopulations of NT and mechanisms of interaction.

2F. Cognition and Behavior

P2-F-121: *Object location learning requires hippocampal CA1 somatostatin interneuron activity and is facilitated by optogenetic long-term potentiation induction.*

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Long-term synaptic network changes underlie hippocampal learning and memory. Activity of CA1 somatostatin interneurons (SOM-INs) during aversive stimulation is necessary for contextual fear memory (CFM). mTORC1 dependent long-term potentiation (LTP) of SOM-IN excitatory synapses from pyramidal cells (PC-SOM synapses) is induced during learning and contributes to CFM. PC-SOM synapses LTP also supports consolidation of spatial memory (SM) in the Barnes maze. However, whether SOM-IN activity and LTP are necessary during acquisition or consolidation of SM remains to be determined. We used optogenetics to examine if SOM-IN activity and LTP during learning are sufficient to regulate object location memory (OLM), a hippocampus-dependent spatial memory task. First, we used dorsal CA1 injection of AAV9.flex.CBA.Arch-GFP.WPRE.SV40 in SOM-Cre mice and found that optogenetic inhibition of SOM-IN during object location acquisition impaired OLM. Second, we used dorsal CA1 injection of AAV-CaMK2a-ChR2 (E123T/T159C)-mCherry in SOM-Cre-eYFP mice and gave an optogenetic induction protocol (TBSopto) for PC-SOM LTP 30 minutes before object location learning. TBSopto resulted in OLM facilitation. In mice with mTORC1 pathway inactivated selectively in SOM-INs (and PC-SOM synapses LTP deficient), TBSopto failed to facilitate OLM. Thus, SOM-IN activity appears necessary for object location learning, and PC-SOM synapse LTP prior to acquisition facilitates OLM, suggesting that SOM-IN activity and plasticity support hippocampus-dependent spatial learning. Funding: CIHR, CRC, CFI, FRQS

P2-F-122: *Cortical microcircuits underlying stress-mediated impairments of working memory*

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Stress impairs cognition in healthy people and worsens cognitive dysfunction in mental illness. The prefrontal cortex (PFC) is a major target of stress, where stress-induced neurochemical changes are proposed to impair working memory. However, specific molecular and circuit mechanisms remain unsolved partly due to the difficulty in assessing working memory in rodents. Past studies primarily used delay tasks in mazes that are robust to delays (>10 s) longer than what is reported in primates, rendering comparing results difficult. To overcome this, we focused on using the touchscreen operant chambers to establish a rodent working memory task that is sensitive to short delays. First, we used the trial unique non-matching to location (TUNL) task to test working memory in male and female mice. Both sexes displayed working memory impairment that was highly sensitive to short delays (1-

5 s). Next, mice were stressed by acutely restraining them for variable durations to alter the stressor magnitude. Interestingly, 1 hour restrain stress enhanced working memory, whereas 4 hours restrain impaired it, pointing to U-shape effect of stress on working memory performance. Further Pharmacology experiments revealed a role for the PFC stress mediator corticotropin releasing hormone (CRH) in working memory alterations. In Summary, touchscreen operant chambers provide a stress-sensitive rodent working memory task that will help dissect the neuronal circuits involved in stress-mediated cognitive impairments.

P2-F-123: *Reduced Temporal Precision in Neural Activity of Schizophrenia*

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Studies of perception and cognition in schizophrenia (SCZ) show neuronal background noise (ongoing activity) to intermittently overwhelm the processing of external stimuli. This increased noise, relative to the activity evoked by the stimulus, results in temporal imprecision and higher variability of behavioral responses. What, however, are the neural correlates of temporal imprecision in SCZ behavior? We first report a decrease in electroencephalography signal-to-noise ratio (SNR) in two SCZ datasets and tasks in the broadband (1-80 Hz), theta (4-8 Hz), and alpha (8-13 Hz) bands. SCZ participants also show lower inter-trial phase coherence (ITPC)-- consistency over trials in the phase of the signal--in theta. From these ITPC results, we varied phase offsets in a computational simulation, which illustrated phase-based temporal desynchronization. This modeling also provided a necessary link to our results and showed decreased neural synchrony in SCZ in both datasets and tasks when compared with healthy controls. Finally, we showed that reduced SNR and ITPC are related and showed a relationship to temporal precision on the behavioral level, namely reaction times. In conclusion, we demonstrate how temporal imprecision in SCZ neural activity--reduced relative signal strength and phase coherence--mediates temporal imprecision on the behavioral level.

P2-F-124: *The effect of early life environmental enrichment on cognitive performance in the triple transgenic Alzheimer's disease mouse model*

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The cognitive reserve (CR) hypothesis posits that individuals with an enriched lifestyle are less susceptible to cognitive decline associated with aging and dementia. CR can be modeled with an

environmental enrichment (EE) protocol which places mice in a large cage with cage-mates, a running wheel, and various objects. However, traditional EE procedures are limited in their ability to quantify individual mouse enrichment. Thus, we developed a novel EE procedure to enable better control and quantification. The current study used male wildtype and 3xTg-AD mice to model CR using this procedure. Mice were assigned to one of the four following conditions following weaning at 5 weeks of age: Environmental Enrichment housing (EH), which is modeled after traditional EE protocols; Enrichment Track (ET), in which mice run laps on an obstacle track 6 days/week with novel obstacles daily; Exercise Control Track (CT), in which mice run laps but are not exposed to complex obstacles; and Standard Housing (SH). Following two months in these conditions, we tested all mice on a task assessing multisensory integration (MSI) abilities, an understudied but potentially important aspect of AD cognitive impairment. The ET groups were the only mice to perform an olfactory-tactile multisensory oddity (MSO) task when tested at 12 months of age, whereas all other groups were impaired. Thus, our results suggest that ET training early in life may confer cognitive benefits related to MSI and that this effect can reverse deficits on the MSO task that relate to AD-like pathology.

P2-F-125: *Neurogenesis mediated plasticity is associated with reduced neuronal activity in CA1 during context fear memory retrieval*

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Adult hippocampal neurogenesis has been demonstrated to affect learning and memory in numerous ways. Several studies have now demonstrated that increased neurogenesis can induce forgetting of memories acquired prior to the manipulation of neurogenesis and, as a result of this forgetting can also facilitate new learning. However, the mechanisms mediating neurogenesis-induced forgetting are not well understood. Here, we used a subregion-based analysis of the immediate early gene c-Fos as well as in vivo fiber photometry to determine changes in activity corresponding with neurogenesis induced forgetting. We found that increasing neurogenesis led to reduced c-Fos expression density in CA1 during context memory retrieval. These results were corroborated by fiber photometry experiments in which neuronal activity in CA1 was decreased during memory retrieval and displayed a less behaviour-specific response during bouts of active memory recall. We also demonstrate that perineuronal net expression in CA1 decreases with increased adult hippocampal neurogenesis. This relationship was found to be bidirectional, in that the density or activity of adult generated neurons in the dentate gyrus was inversely related to the density of perineuronal nets in CA1. These results suggest that neurogenesis may induce forgetting by disrupting perineuronal nets in CA1 which may otherwise protect memories from degradation.

P2-F-126: *The supramammillary nucleus (SuM) integrates environmental signals and modulates mood and cognition via regulation of hippocampal neurogenesis*

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Adult neurogenesis in the dentate gyrus (DG) of the hippocampus represents an important form of neuroplasticity that regulates both mood and cognition. Adult neurogenesis is bidirectionally regulated by environmental stimuli, including enrichment (which promotes neurogenesis) and stress (which suppresses neurogenesis). However, how these signals reach the DG to regulate neurogenesis is unknown. To address this, we used anatomical tracing to identify input projections to the DG from cortical, basal forebrain, midbrain and hypothalamic regions. We found that the activity of many of these regions was regulated by environmental enrichment and stress. In particular, the activity of one hypothalamic region, the supramammillary nucleus (SuM), was downregulated by chronic enrichment and upregulated by chronic restraint stress. The SuM sends both excitatory and inhibitory projections to the DG. We found that chronic chemogenetic inhibition of SuM excitatory (but not inhibitory) projections increased neurogenesis, similar to enrichment. Conversely, chronic activation of these same SuM projection neurons suppressed neurogenesis, similar to stress. Subsequent experiments established that these effects are mediated by an SuM (excitatory neuron) to DG (granule cell) to DG parvalbumin (PV) interneuron circuit, and that chemogenetic interventions targeting this circuit can mimic or block the effects of environmental signals on neurogenesis. Finally, we show that direct manipulation of SuM has bidirectional effects on mood and cognition, similar to enrichment and stress manipulations. Together, these studies identify the SuM as a key region that translates environmental signals into effects on mood and cognition via regulation of hippocampal neurogenesis.

P2-F-127: *Rapid effect of 17b-estradiol in the paraventricular nucleus on social recognition in male mice*

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Estrogens and oxytocin (OT) play important roles in the mediation of social recognition (SR). It has been hypothesized that estrogens and OT interact to mediate SR, by estrogens binding to the estrogen receptors in the paraventricular nucleus of the hypothalamus (PVN) to facilitate OT production and release. The OT then reaches the medial amygdala (MeA), which also receives direct projections from

the olfactory bulbs, and bind to the OTR to allow incoming olfactory information to be used for SR. We have tested this interaction in ovariectomized female mice and if it occurs through estrogens' rapid mechanisms. 17β-estradiol (E2) infusions into the PVN rapidly facilitated SR and infusions of an OTR antagonist into the MeA blocked this rapid facilitation of SR by E2 infused into the PVN. These findings show support for the rapid estrogen/OT interaction on SR. The current experiment is testing whether this interaction also occurs in male mice. E2 was infused into the PVN of castrated male mice and tested in a rapid SR paradigm. We have found that E2 doses of 25, 50, and 100nM in the PVN do not rapidly facilitate SR in male mice. We are currently testing 2 additional doses, 10 and 200nM, as it is possible that a dose outside of the range found to be effective in females is effective in males. If these doses also show no facilitating effect on SR, it suggests that E2 in the PVN of male mice doesn't facilitate SR and that the rapid estrogen/OT interaction mediating SR is sex-specific, only occurring in female and not male mice. Funded by NSERC.

P2-F-128: *A complex interaction between sex steroids and vasopressin in the bed nucleus of the stria terminalis rapidly modulates social recognition and aggression in male mice*

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Sex steroids can affect social recognition and aggression by rapidly interacting with other neuropeptides such as arginine-vasopressin (AVP). The AVP system includes sexually differentiated brain regions, bed nucleus of the stria terminalis (BNST) and lateral septum (LS). The steroids/AVP interplay is involved in social behaviours, although the underlying mechanisms are yet to be understood. To elucidate the rapid effects of sex steroids on SR, adult castrated (CX) male mice were infused with different doses of Testosterone (T), 17β-estradiol (E2) or dihydrotestosterone (DHT), in the BNST. SR was then assessed by a 'difficult' paradigm, in which CX mice are impaired. To assess aggression, mice were tested in a resident-intruder paradigm at either 35- or 120-min post-infusion to evaluate rapid and long-lasting effects. Next, to investigate the steroids/AVP interplay, CX male mice received infusions of a specific antagonist for the AVP receptor 1a (α-VR1a) in the LS 5 min prior to T, E2, or DHT in the BNST. Results revealed that infusing T, E2, or DHT in the BNST facilitated SR, with treated CX mice spending more time investigating a novel over a familiar CX mouse. In addition, all 3 steroids increased the dominance score at 35-min, but only T and E2 increased it at 120-min. The infusion of α-VR1a in the LS prevented the facilitating effects of T or E2 in the BNST, but not those of DHT. These results confirm the existence of a BNST-LS circuit involved in SR and reveal a complex interaction between sex steroids and AVP.

P2-F-129: *The role of mPFC projection-specific populations in recent and remote expression of memories*

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Memories are known to initially depend on the hippocampus for expression, but become more dependent on the medial prefrontal cortex (mPFC) at remote time-points. Although retrieval-induced activity of mPFC neurons increases with time, it is unclear whether distinct mPFC projection-specific populations (PSPs) contribute to retrieval at different time points. Here, we explored how distinct PSPs of mPFC contribute to memory expression at recent vs. remote time-points. To do this, we virally labeled PSPs of mPFC and examined the extent to which they are activated during contextual fear learning, and subsequently reactivated during recent vs. remote recall. Then, we used optogenetics to either reactivate or silence these PSPs to assess their contribution to the recall at different time-points. Our results indicate that distinct mPFC PSPs differentially contribute to recent vs remote recall. In particular, the PSPs that target basolateral amygdala (BLA) or retrosplenial cortex contribute to recall at recent and remote time-points, while PSPs that target nucleus reuniens (NRe), nucleus accumbens (NAc), or paraventricular nucleus (PV) contribute more to remote recall. Furthermore, the remote engagement of the NRe projecting neurons lead to a decreased hippocampal activity in CA1 region. Together, at recent time-point, a limited engagement of mPFC is observed (e.g. BLA or RSC) while at remote time-point the mPFC's engagement is enhanced by recruiting additional PSPs (e.g NRe, NAc, and PV). This enhanced engagement is associated with decreased activity in CA1 region which suggests a top-down regulatory mechanism by mPFC on hippocampus during remote recall of memories.

P2-F-130: *The roles of sex and menstrual cycle phase in mapping out human spatial navigation strategies and performance*

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Our objective was to understand if sex and menstrual cycle influence the human ability to navigate and orient in spatial surroundings. As ovarian hormones affect the hippocampus, we hypothesized that navigation behaviour would be influenced by both variables. To address this hypothesis, we undertook an online study of reproductive age women and men, asking them to demonstrate and self-report their spatial navigation skills and strategies. Participants self-reported their sex and current

menstrual phase (early follicular (EF), late follicular/periovulatory (PO), and mid/late luteal (ML)), and completed a series of tasks measuring topographical memory, facial recognition, path/location integration, and cognitive map use. As predicted, we found that sex influenced facial recognition, path integration, and self-reported use of cognitive map and scene-based strategies. Menstrual phase moderated the influence of sex: Compared to men, women had better facial recognition, worse path integration, and reported using scene-based strategies more, but only during the PO phase; women in the PO phase were also better at location integration than both women in the EF phase and men. These findings provide evidence that human spatial navigation and facial recognition processes are affected by the menstrual cycle.

P2-F-131: *Astrocytes are star participants in the effects of early-life stress on cognitive dysfunction*

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Adverse childhood experiences are associated with an enhanced susceptibility to the development of mood disorders, such as major depressive disorder (MDD). The lateral amygdala, a brain region important for emotive and cognitive behaviours is vulnerable to the effects of early-life stress (ELS). However, the mechanisms by which ELS impairs behaviour are poorly defined. Previously, research has focused on the neuronal mechanisms underlying stress-induced behavioural impairments, however the role of glial cells in this circuitry remains undetermined. Hence, we aimed to identify the role of astrocytes in the effects of ELS on lateral amygdala-dependent behaviour. To accomplish this, we used a rodent model of maternal abuse and neglect to replicate the effects of ELS on the developing brain, in combination with genetic manipulations of astrocytes and behavioural testing. ELS significantly impaired threat-detection, a cognitive process involving the ability to accurately distinguish between a previously learned threatening tone and a non-threatening tone in a novel context. Interestingly, genetic manipulations to induce astrocyte network dysfunction impaired threat detection in male mice. Additionally, decreasing astrocyte stress sensitivity by deleting astrocyte glucocorticoid receptors significantly enhanced cognitive function in both ELS and naïve mice. Overall, our results suggest that astrocytes are central regulators of the effects of ELS on cognitive impairment. This data highlights astrocytes as potential therapeutic targets for cognitive dysfunction, a pervasive symptom associated with mood disorders.

P2-F-132: *Optimization and characterization of an ischemic model of the nucleus accumbens in male mice*

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One-third of stroke survivors develop post-stroke depression (PSD). Intriguingly, lesions to the left basal ganglia, which include the nucleus accumbens (NAc), have been linked to increased PSD prevalence. Alterations of the NAc-related circuitry contribute to maladaptive stress responses and human depression but, to date, very few studies investigate this brain region in the context of PSD. We hypothesize that an ischemic lesion in the NAc may favor a depressive-like phenotype. Indeed, we showed that NAc neurovascular alterations are associated with vulnerability to stress exposure. Here, we optimized and characterized the impact of a NAc ischemic lesion with endothelin-1 (ET-1), a vasoconstrictive peptide. Stereotaxic coordinates and optimal volume of ET-1 injection were first defined then effects on gene expression were evaluated. These molecular studies were complemented by morphological assessments and behavioral tests related to anxiety- and depression-like behaviors. This model produced a typical ischemic lesion with neuronal loss and massive astrocytes and microglia activation. Cresyl violet stain revealed a maximal lesion at 1-day post-surgery, still present at day 3, filled with cells after 1 week, and barely visible at 2 weeks. Changes in endothelial and glial gene expression were observed accordingly. We are currently performing a battery of behavioral tests in male mice subjected or not to stress exposure. This project will expand basic knowledge on the vascular biology underlying ET-1-driven ischemic insult and the possible role of the NAc in PSD.

P2-F-133: *A feedback inhibition motif involved in an action sequence in Drosophila larval escape behavior*

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Each animal possesses many behaviors for survival such as communication, courtship, and prey capture. Such behaviors consist of mutually exclusive actions that are often processed in defined sequences. However, how the nervous system executes action sequences remains unclear. Thus, I proposed to illustrate the mechanism of action sequences by studying Drosophila larval escape response. Drosophila larvae display a rigid escape response, rolling followed by fast crawling. These two actions could be triggered independently, complying with hierarchical suppression theory claiming that different actions are activated parallelly and inhibit each other to compete. Another feature of this theory is that actions terminate themselves to allow the execution of other actions. To examine the neural mechanism underlying this larval escape sequence and test if it agrees with the hierarchical suppression model, I synchronized the optogenetic activation of escape-triggering

neurons, Basins, and some unknown neurons to interrupt the escape response. In this screen, a group of neurons, composed of mushroom body neurons and a pair of inhibitory descending neurons named SeIN128, was found to terminate rolling, but they didn't affect fast crawling. Except that the onset of fast crawling got earlier, which might be caused by the earlier offset of rolling. Neuron reconstruction showed that SeIN128 receives inputs from and sends outputs to the escape circuitry. Thus, this finding could be the circuit evidence of feedback inhibition of rolling which encodes self-termination, one of the features of hierarchical suppression theory.

P2-F-134: *Lactate metabolism in the fly brain influences aging and long-term courtship memory*

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Cognitive processes are metabolically costly. Aging promotes the deterioration of many brain and bodily functions that are intricately tied to energy consumption, including cognition. Several studies in vertebrates have implicated the astrocyte-neuron lactate shuttle in long-term memory. The importance of brain metabolism in long-term aversive olfactory memory has also been examined in the fruit fly Drosophila melanogaster. However, previous studies investigated the use of glial glucose and ketone bodies as fuel for neurons but did not test for aging and the contribution of lactate. Our work aims to directly investigate the role of lactate metabolism in relation to aging and long-term memory in flies. We genetically manipulated Drosophila lactate dehydrogenase (dLdh) expression in either neurons or glia within the adult phase of life, and tested males for age-related decline in survival, climbing ability, and long-term courtship memory. Interestingly, we found deficits in long-term courtship memory only in aged flies which did not directly corelate with decreased survival and climbing ability. Furthermore, we uncovered age-related changes in the accumulation of neutral lipids, lactate, pyruvate, 2-hydroxyglutarate and TCA cycle intermediates within the brain of flies with altered dLdh expression within glia or neurons. Our findings provide motivation for further study of neuron-glia metabolic coupling in the brain by shedding light on the intersection between neuron-glia lactate shuttling, aging, and memory in Drosophila.

P2-F-135: *The effects of ketamine in a ZnT3 KO mouse model of chronic stress*

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Major depressive disorder (MDD) is a severe mood disorder that is commonly treated with antidepressants; however, one third of patients with MDD do not respond to current therapies. Interestingly, it has been found that people with depression have reduced levels of zinc, and zinc supplements can improve their depressive symptoms, potentially through its actions as a neurotransmitter. This phenomenon is facilitated by zinc transporter 3 (ZnT3), which packages zinc into synaptic vesicles. Using a ZnT3 knockout (KO) mouse model that lacks vesicular zinc, we sought to investigate the interplay between vesicular zinc, chronic stress, and ketamine as a novel therapeutic for treatment-resistant depression, which has been shown to display rapid and sustained antidepressant-like effects. Wildtype (WT) and ZnT3 KO mice were subjected to multiple simultaneous acute stress or kept under standard housing conditions, then administered ketamine or saline. Preliminary behavioural analyses revealed that among stressed mice administered saline, ZnT3 KO mice displayed more depressive-like behaviours during the open field test and elevated plus maze, compared to WT mice. Additionally, greater depressive phenotype was observed in mice administered saline compared to ketamine during the splash test, regardless of stress condition and genotype. Sex had no effect on depressive phenotype. Collectively, these findings support the role of vesicular zinc in depressive-like behaviours, and suggest the effectiveness of ketamine as an antidepressant-like therapeutic for patients with MDD.

P2-F-136: *eIF4G1-mediated translational control is required for mitochondrial oxidative phosphorylation and hippocampus-dependent learning and memory*

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Protein synthesis is a critical step in gene expression, and it has been extensively studied in a variety of biological processes, including synaptic plasticity and cognitive functions. Translation initiation, known as a rate-limiting step in protein synthesis, is regulated by initiation factors: eIF2-GTP-Met tRNAi ternary complex and eIF4F. eIF4F is composed of cap-binding protein eIF4E, ATP-dependent RNA helicase eIF4A, and scaffold protein eIF4G and is responsible for recruiting ribosomes to the initiation codon of mRNA. eIF4G1, a major form of eIF4G, is indispensable for early development, but whether and how eIF4G1-dependent mRNA translation is implicated in brain functions remains poorly understood. To study the role of eIF4G1, we used eIF4G1 haploinsufficient (eIF4G1-1D) mice generated by CRISPR/Cas9. These mice were intact in general behavior but impaired in hippocampus-dependent learning and memory. Translatome profiling using early postnatal forebrains showed that the translation efficiency of mitochondria-encoded oxidative phosphorylation (OXPHOS) genes is decreased in the eIF4G1-1D brain while global translation is not altered. Consistently, mitochondrial membrane potential (ΔΨm) and ATP level in eIF4G1-depleted cells were reduced. The axonal

branching of in vitro cultured eIF4G1-1D hippocampal neurons was significantly disrupted, implying a possibility of abnormal neural connectivity in the eIF4G1-1D brain. Taken together, these results demonstrate that eIF4G1-mediated translational control is crucial for OXPHOS, neuronal development, and cognitive functions.

P2-F-137: *Establishing a role of the semantic control network in social cognition: a meta-analysis of functional neuroimaging studies*

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The contribution and neural basis of cognitive control are under-specified in many prominent models of socio-cognitive processing. Important outstanding questions include whether there are multiple, distinguishable systems underpinning control and whether control is ubiquitously or selectively engaged across different social behaviours and task demands. Recently, it has been proposed that the regulation of social behaviours could rely on brain regions specialised in the controlled retrieval of semantic information, namely the anterior inferior frontal gyrus (IFG) and posterior middle temporal gyrus. We, therefore, set out to investigate for the first time whether the neural activation commonly found in social functional neuroimaging studies extends to these 'semantic control' regions. We conducted five coordinate-based meta-analyses to combine results of 499 fMRI/PET experiments and identified the brain regions consistently involved in semantic control, as well as four social abilities: theory of mind, trait inference, empathy and moral reasoning. This allowed an unprecedented parallel review of the neural networks associated with each of these cognitive domains. The results confirmed that the anterior left IFG region involved in semantic control is reliably engaged in all four social domains. This finding supports the hypothesis that social cognition is partly regulated by the neurocognitive system underpinning semantic control and has implications for models of both neurotypical and disordered social cognition.

P2-F-138: *Sex differences in the acquisition of Pavlovian cue-directed behaviour elicited by morphine on a single-trial basis*

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Introduction: Interoceptive signals from drugs of abuse play an essential role in developing Pavlovian drug-cue associations. Prior investigations have shown potential sex differences in acquiring both

appetitive and inhibitory Pavlovian feature positive (FP) and negative (FN) associations, respectively, with morphine as the occasion setter; however, their methodologies assess behaviour only at the beginning of each multi-trial session. The present study aimed to assess acquisition behaviour after every CS-US pairing to better track learning patterns by sex and contingency. Methods: Male and female rats were assigned to FP or FN groups and received 96 daily intermixed morphine (3.2 mg/kg) or saline injections prior to a 4-minute session with a single 15s white noise (WN) presentation. For FP rats, WN on morphine sessions was followed by 4s access to 0.1 mL of 26% sucrose solution, and FN rats had no access. Saline indicated sucrose access for the FN rats and no access for FP rats. Results: Preliminary results indicate acquisition under both contingencies and sexes; however, FN rats showed a gradual emergence of the discrimination with significant Drug x Session interactions and main effects of Drug, whereas FP rats showed only main effects of Drug. This main effect of Drug was more pronounced in male than female FP rats. Conclusions: Standard training for Pavlovian drug discrimination uses multi-trial sessions that obfuscate assessment of trial-by-trial learning. Here we demonstrate such learning can be investigated and may be influenced by contingency and sex.

P2-F-139: *Effect of the bacterial product, Propionic Acid, on Habituation to Social and Non-Social Odours by Adult Male Rats.*

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Disturbances involving metabolites of the gut microbiome play a role in the etiology of autism spectrum disorder (ASD). The short-chain fatty acid, propionate (PPA), is of interest as it can cross both the gut-blood and blood-brain barriers and have central effects. ASD may contribute to social deficits through impaired habituation to sensory and social stimuli. The present study examined the effects of systemic injections of PPA in adult male rats on habituation to social and non-social odors. Each day, rats were given intraperitoneal injections of 500 mg/kg PPA, or phosphate buffered saline (PBS). On the baseline day, rats were exposed to clean bedding. To examine habituation, over the next 3 test days, rats were repeatedly exposed to a social odor from a stranger rat's bedding, or a non-social odor of vanilla extract. On the last test day, a novel odor was introduced, either from an unfamiliar rat for social groups, or almond extract for non-social groups. Behavior was recorded while rats were in a 2-chambered open-field (OF), with the odor in a petri dish in one chamber, and the other chamber empty. The OF apparatus detected all vertical and horizontal activity while self-grooming, approach toward the odor and sniffing of the odor was manually scored from videos. PPA rats showed hypoactivity as well as significantly more self-grooming than PBS rats across baseline and test days. The PPA social group showed trends of reduced habituation compared to the PBS social group for number of entries and approach towards the odor exposure area. PBS rats also showed higher dishabituation than PPA rats on the final test day when the novel odor was introduced. These results

suggest that PPA may contribute to social deficits in ASD by impairing habituation to sensory social cues.

P2-F-140: *Neural and behavioural correlates of accidental cannabis poisoning*

Richard Quansah Amissah[1], Hakan Kayir[1], Asfandyaar Talhat[1], Jibran Khokhar[1]

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Accidental exposure to Δ9-tetrahydrocannabinol (THC) cannabis edibles is common in children and pets; however, its neural and behavioral correlates are unknown. We examined the effects of acute high-dose THC edible administration on neurons and behavior in rats. A cohort of rats was implanted in the prefrontal cortex (PFC), dorsal hippocampus (dHipp), cingulate cortex (Cg), and nucleus accumbens (NAc) and exposed to a mixture of Nutella (6 g/kg) and THC (20 mg/kg). Subsequently, cannabis tetrad and neural oscillations were examined after 2, 4, 8, and 24 hrs. In another cohort, we examined the effects of high-dose THC on learning (active avoidance learning) and sensorimotor gating (acoustic startle reflex) and the plasma THC and 11-hydroxy-THC (11-OH-THC) concentrations. High-dose THC resulted in hypolocomotion, hypothermia, and analgesia, but not catalepsy. It also reduced high gamma (□) power in all 4 regions, reduced low □ power only in the PFC, NAc, and dHipp, and decreased Cg-dHipp and PFC-dHipp low and high □ coherence. Compared to control rats, THC rats were unable to learn to avoid foot shock in the active avoidance task and had reduced prepulse inhibition. Finally, there was a steady decrease in plasma THC and 11-OH-THC levels, with the highest levels at the 4-hr time point. Our results suggest that acute high-dose THC exposure results in significant behavior and neural changes that last for 24 hrs after exposure. Most of these changes appear after 4 hrs, suggesting that there might be a window for interventions aiming to reduce the effects of poisoning from accidental acute high-dose THC consumption.

P2-F-141: *The effect of feeding frequency in rearing tanks on the behaviour of adult zebrafish in an appetitive conditioning paradigm*

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Associative learning is often studied using food as a reward (US). In zebrafish, however, food reward has been employed with varied success. Satiation with food may render the rewarding value of this US limited. With warm-blooded species, the solution has been to reduce body weight, thus making the subject hungrier and more motivated. We, however, observed the opposite with zebrafish. Here, we provide evidence, for the first time, that increased feeding improves motivation to obtain food in

learning tasks in zebrafish. We assigned zebrafish randomly to 2 groups. In group 1 fish were fed once a day (food-deprived). In group 2, fish were fed 5 times a day, i.e., 5 times the amount (well-fed) every day for 3 months. Subsequently, we paired food (US) with a red cue card (CS) placing these stimuli together in one arm of a plus-maze. We also run an unpaired task, in which the CS and US were presented randomly. Unlike with mammals, we found well-fed zebrafish to consume more food throughout all trials compared to the food-deprived ones. Furthermore, well-fed fish in the paired group swam significantly closer to the CS during a post-training probe trial compared to the well-fed unpaired group. Whereas food-deprived fish showed no effect of pairing vs unpairing the CS-US. In sum, feeding the fish well led to improved food consumption and improved learning performance in our food rewarded task in zebrafish.

P2-F-142: *Decoding rodent behavioural strategies for navigating object-location associations*

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Flexible navigation depends centrally on the hippocampal system. Typical laboratory rodent behavioural experiments are designed to isolate a specific behavioural or cognitive process; a well-designed task presents a specific challenge to be solved in a certain way (i.e., win-shift vs. win-stay strategies). Despite these efforts, detailed accounts of behaviour often yield evidence that animals develop a variety of strategies to solve the same task. Cognitive tasks that require weeks of training are especially prone to exhibit heterogeneity in behavioural strategies between animals. A clear and quantifiable account of this heterogeneity is necessary to link the behaviour of individual subjects to genetic and circuit manipulations, neuronal coding schemes, therapeutic studies to enhance or restore cognition. Here, we aim to link neuronal coding in the hippocampus to heterogeneities in behavioural strategies employed by mice in an object-location paired associate learning (PAL) touchscreen task. We modified the PAL task to include within-session 'probe trials' to assess behavioural strategy, which revealed hidden behavioural states across mice not reflected in traditional percent correct performance metrics. One-photon calcium imaging of large neuronal populations in dorsal CA1 with miniscopes demonstrate that heterogeneity in trial-type specific spatial tuning coincided with performance on strategy-probing trials. These data suggest that object-location representations in the hippocampus are best modeled by hidden states that reflect particular behavioural strategies.

P2-F-143: *Adolescent cannabis vapour exposure alters pavlovian sign-tracking behaviours in adulthood.*

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There have been dramatic increases in adolescent cannabis vaping in recent years; however, the long-term effects of this exposure are unknown. This study aimed to experimentally investigate the effects of chronic cannabis vapour exposure during adolescence, on Pavlovian reward learning in adulthood. The cannabinoid tetrad test and plasma cannabinoid assessment were used to confirm adequate adolescent cannabis exposure. Three groups of male adolescent Sprague-Dawley rats (n=7/group) were exposed to either cannabidiol (CBD), D-9-tetrahydrocannabinol (THC), or balanced THC+CBD from post-natal day (PND) 28-42. On day 7, rats were subject to the tetrad test at 0h, 2h, 4h, and 20h after exposure. Plasma samples were collected pre- and post-exposure on day 14. In adulthood (PND68), rats were subjected to 18 days of sign-tracking, where a sucrose pellet reward was delivered after the appearance of the conditioned stimulus (CS+) lever, regardless of the rat's interaction with it. All 3 groups displayed a statistically significant change in at least 1 component of the tetrad (locomotion, hypothermia, tail-flick analgesia, catalepsy), as well as significantly higher THC or CBD plasma concentrations (ng/ml) post-exposure. Sign-tracking performance showed significant differences between all 3 groups; balanced THC+CBD showed the highest CS+ lever presses, followed by the THC group, and then the CBD group. This supports our hypothesis that THC exposure in adolescence would result in significantly higher sign-tracking than CBD alone- indicating a long-lasting, impact on reward learning.

P2-F-144: *Determining the role of perirhinal parvalbumin-containing GABAergic inhibitory interneurons on category learning using a mouse object category recognition (OCR) task*

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Accurate object category recognition may rely on the use of generalized category representations which could be refined with inhibitory GABAergic signalling. Previously we demonstrated that disrupting GABAergic transmission impairs category learning on a mouse object category recognition (OCR) task. Parvalbumin-containing GABAergic inhibitory interneurons (PVINs) have been implicated in the refinement of cortical representations of visual stimuli. PVINs provide feedforward inhibitory control in perirhinal cortex (PRh), an area which is necessary for object recognition and feature-binding. To determine the role of PRh GABAergic PVINs in the formation of generalized category representations, we infused male PVcre mice intracranially with adeno-associated virus containing either an excitatory or inhibitory designer receptor exclusively activated by designer drugs (DREADDs). The DREADD agonist 21 (C21) was administered systemically (i.p., 1mg/kg) prior to exposure to object category exemplars. Prior exemplar exposure is required to perform the OCR task with a 1-h delay. Both inhibition and stimulation of PRh PVINs prior to pre-exposure sessions impaired OCR task

performance with a 1-h, but not a 30-min, retention delay. With a 30-min retention delay, which does not require category familiarity, task performance was also disrupted by pre-sample PVIN stimulation. These findings suggest that PVIN activity in PRh plays an essential role in the refinement of object category representations for long-term memory, as well as encoding of object information.

P2-F-145: *Assessing post-stroke motor impairment and recovery using an automated skilled reaching task in mice*

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Accurate assessment of sensorimotor function in rodent models of stroke is essential for understanding how brain reorganization or plasticity contribute to functional recovery after stroke. We recently developed the Home-cage Automated Skilled Reaching Apparatus (HASRA) that allows automated training and assessment of mice engaged in a skilled reaching task. To validate the HASRA as a sensitive tool for assessing post-stroke performance, group-housed mice were trained on the reaching task for 14-21 days, followed by an M1 photothrombotic stroke or sham procedure. Mice were immediately returned to the HASRA and performance was monitored for 4 weeks. Performance at baseline, the initial impairment period (post-stroke days 1-3), and the residual impairment period (post-stroke days 27-29) was compared. Stroke mice had a significantly reduced performance days 1-3 post-stroke compared to baseline but had some improvement by days 27-29 post-stroke. We divided the stroke mice into two groups: 1) mice that achieved a higher mean success rate and 2) mice with a lower mean success rate at the residual impairment period. Through binomial logistic regression analysis, we found that baseline performance, lesion location, and the time spent by the mice engaging with the reaching task post-stroke were significant predictors of the mice's performance by the residual impairment period. Overall, having automated tools, such as the HASRA, for accurately quantifying stroke-related motor impairments and recovery is essential for assessing the efficacy of potential stroke therapies.

P2-F-146: *Glutamatergic afferents to the nucleus accumbens integrate outcomes in reward-learning*

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Alterations in reward learning are associated with psychopathologies such as depression. The nucleus accumbens (NAc) is implicated in motivation and reward as well as depression, integrating input from a range of afferents including the ventral hippocampus (vHip) and the medial prefrontal cortex

(mPFC). However, the role of these glutamatergic inputs to the NAc in reward learning remains relatively unexplored. Using frame-projected independent-fiber photometry, we recorded population-level activity of NAc afferents from the mPFC and the vHip in male and female mice in a two-armed bandit task. We find that both neural projections dynamically encode information about trial outcome and outcome history, with notable pathway specific time-dependent trajectories. Rewarded vs non-rewarded outcomes are associated with suppression in the mPFC and vHIP following a choice, with vHIP suppression emerging at a longer delay following choice. Additionally, we found relationships at multiple time points between neural activity and several reward learning metrics, further implicating these projections in tracking outcomes over time. Together, these findings demonstrate that mPFC and vHip projections to the NAc integrate outcomes over time in reward learning. Given evidence implicating these pathways in depression-like states, our results may suggest that these neural circuits could contribute to alterations in reward learning observed in psychopathologies.

P2-F-147: *Pathophysiology of retrosplenial cortex in acute and chronic pharmacological models of cognitive impairment in schizophrenia*

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Schizophrenia (SCZ) is a severe, chronic disorder that manifests with psychopathological symptoms that include positive, negative, and cognitive symptoms. Cognitive impairment in SCZ is debilitating and associated with substantial disruptions in the default mode network (DMN). As a heavily interconnected brain region and a major node of the DMN, retrosplenial cortex (RSC) is involved with a range of cognitive functions including memory and spatial navigation. However, dysfunction in RSC at the cellular and network level in SCZ has not been well described. In the current study, we explored cognitive impairment after acute or chronic ketamine administration in mice, and related impairments to pathophysiology using in vivo imaging and immunohistochemistry. Male and female C57/BL6 wild-type animals were treated with acute or chronic (14 days) treatment with ketamine (30mg/kg, or vehicle control), both of which induced cognitive dysfunction, including impairment in spatial and non-spatial cognitive tasks. To relate impairment to alterations in neuronal and glial physiology, in vivo two photon microscopy was employed. By imaging Thy1-GcAMP6s transgenic mice, altered neuronal spiking and changes in local neuronal functional connectivity in RSC were observed after acute and chronic ketamine. Greater activation of microglial cells was observed in RSC in vivo (using CXCr3-GFP mice) and using immunohistochemistry after chronic treatment. Future studies will relate changes in neuronal and glial activity to degradation of perineuronal nets (PNNs) enwrapping PV interneurons in the RSC.

P2-F-148: *Uncovering an aversive component of dopamine neuron self-stimulation*

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Dopaminergic inputs to the ventral striatum support self-stimulation behaviour and paradoxically these same inputs, at times, signal aversion and produce avoidant behaviours. To investigate the interplay between these rewarding and aversive components, we developed a novel self-stimulation procedure in which mice are trained to hold-down a lever for continuous self-stimulation. When we used lever hold-downs to trigger photostimulation of dopamine fibers in the ventral striatum, the mean duration of self-stimulation was about 3 seconds. This behaviour varied according to the within-bout frequency of stimulation. When we altered the stimulation frequency across 30 second intervals, we saw more rapid disengagement from higher frequency stimulations, even though they were more reinforcing. Cumulative time spent holding-down the active lever was highest for 40 Hz and lowest for 2.5 Hz trials, while mean hold-down duration was shortest for 40 Hz trials and longest for 2.5 Hz trials. The divergence of these measures suggests that there may be an aversive component to high frequency DA fiber stimulation. Pharmacological modulation of neurotransmission at D1 but not D2 receptors eliminated the divergence between cumulative and mean hold-down durations. Collectively, these results suggest that high frequency stimulation of ventral striatal dopamine inputs acquires aversive properties through a D1-receptor mediated process which mice mitigate by rapidly terminating stimulation trains.

P2-F-149: *Effect of bupropion on conditioned memory modulation*

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Our group recently demonstrated that post-training exposure to a conditioned stimulus (CS) predictive of foot-shock in rats trained on a two-way signaled avoidance task enhanced memory consolidation by activating dopaminergic and adrenergic receptors. Therefore, it is likely that the ability of emotionally arousing CSs to facilitate memory consolidation depends on enhanced monoamine signaling. To test this hypothesis, we employed a signalled active avoidance procedure (30 trials/session; 0.8 mA) and tested the effect of the avoidance CS in the absence of foot-shock after a single session of avoidance training on the consolidation of object recognition (OR) memory (sample and choice phases separated by 72 hrs) in male Sprague-Dawley rats. It was found that immediate post-sample exposure to the avoidance CS did not modulate OR memory consolidation. However, preliminary results indicated that post-sample administration of the monoamine reuptake inhibitor

bupropion (BUP; 10 and 30 mg/kg) just prior to CS exposure facilitated OR memory without impacting other conditioned responses (i.e., freezing). Importantly, post-sample administration of BUP by itself had no effect on consolidation of OR memory, indicating that BUP and the avoidance CS acted synergistically to impact memory. If these results will hold replication currently ongoing, they would strongly support the hypothesis that CSs activate monoamine neurotransmitters in the brain to influence memory consolidation.

P2-F-150: *What link between 5-HT raphe - ventral hippocampus pathway and aversive behaviors?*

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Even though serotonin (5-HT) strongly modulates emotions, the precise mechanisms through which serotonergic neurons are recruited and how they react to an aversive environment remains to be determined. In particular, the ventral hippocampus (vHP) has also been involved in emotional behaviour and is enriched with serotonergic fibers. Thus, the serotonergic raphe - vHP pathway is ideally positioned to modulate emotional behaviours. This study aims at investigating how the activity of serotonergic neurons changes to adapt to aversive situations. Our objectives are 1- to analyze the correlation between 5-HT neural dynamics and fear or anxiety-like behaviors and 2- to investigate the impact of optogenetic activation of vHP-projecting serotonergic neurons on these behaviors. We used viral strategies in SERT-cre mice to enable conditional expression of the fluorescent calcium sensor GCaMP6s in vHP-projecting 5-HT neurons to perform fiber photometry recordings during exploration of aversive environments. Moreover, the opsin ChETA was conditionally expressed in SERT-cre mice to photoactivate the 5-HT raphe - vHP pathway during anxiety tests or fear conditioning. We found that the activity of serotonergic neurons is modulated during exploration of an aversive environment and that activation of vHP-projecting 5-HT neurons increases anxiety-like behaviors in female but not male mice. This research will provide a deeper insight into the neuronal circuits underlying emotional behaviors to adapt to aversive situations.

P2-F-151: *Identifying and manipulating a hippocampal engram supporting a spatial rewarding memory*

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Previously acquired information is thought to be stored in ensembles of neurons (or engrams). Most rodent engram studies have focused on conditioned fear memory and show that neurons involved in an engram ('engram neurons') are both necessary and sufficient for memory-guided freezing behavior. Whether these findings generalize to other types of memory are unknown. Here we examined how CA1 pyramidal hippocampal neurons are allocated to an engram supporting a specific spatial rewarding memory and whether artificial reactivation of an engram is necessary and sufficient for memory-guided behavior. Mice were trained to navigate towards an un-marked predetermined area of an open field to receive rewarding brain stimulation using spatial cues. Before training, a random sparse subset of CA1 neurons were optogenetically excited to allocate these neurons to the engram supporting this memory. Inhibition of these neurons disrupted subsequent memory retrieval. To examine sufficiency of these allocated neurons to the spatial memory, we tested mice in an impoverished environment in which some of the distal visual cues were removed. Control mice showed disrupted spatial memory upon cue removal. However, mice in which the allocated neurons were optogenetically reactivated showed intact spatial memory. Together, these results indicate that neurons with higher excitability in the CA1 of dorsal hippocampus are preferentially allocated to an engram supporting a rewarding spatial memory and that these neurons influence the complex sequences of actions in pursuit of this goal.

P2-F-152: *Sex-specific effects of chronic stress on intestinal health and depression-like behaviours*

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Major depressive disorder (MDD) is the leading cause of disability worldwide, however, 30-50% of patients are unresponsive to commonly prescribed antidepressants highlighting untapped biological mechanisms. Dysfunction in the "microbiota-gut-brain axis", the bidirectional communication between the central nervous system and the gastrointestinal tract, has been implicated in MDD pathogenesis. We recently underlined stress-related changes in blood brain barrier (BBB) integrity, however, limited investigations examine intestinal barrier function in these conditions. We study the effects of chronic stress on the microbiome and intestinal barrier permeability in male and female mice. We hypothesize that stress induces changes to gut barrier integrity in a sex-specific manner, playing a role in stress response. Accordingly, mice were subjected to chronic social defeat or variable stress paradigms followed by analysis of fecal microbial composition and gene expression profiles of intestinal barrier-related proteins. We observed altered microbial populations as well as changes in gene expression of intestinal tight junctions depending on the type and duration of stress, with sex-

specific effects. Furthermore, certain tight junction changes were associated with depression-like behaviours. Our results provide evidence of chronic stress effects in disrupting intestinal barrier homeostasis in conjunction with the manifestation of depression-like behaviours. Therefore, lowering stress-related peripheral effects on the gut-brain axis may promote stress-resilience in the context of MDD.

P2-F-153: *Episodic-like memory related activity of hippocampal VIP interneurons in freely behaving mice*

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In the CA1 hippocampus, vasoactive intestinal polypeptide (VIP) expressing interneurons primarily comprise disinhibitory cells that selectively innervate GABAergic cells, allowing them to control information flow onto excitatory neurons. CA1 VIP interneurons have been shown to aid spatial learning and memory but their role in episodic memory remains unknown. To address this, we used a series of behavioral tasks to study various facets of episodic memory and simultaneously performed in vivo calcium imaging of dorsal CA1 VIP interneurons using wireless fiber photometry in freely moving mice. We found that VIP interneurons were routinely active during spontaneous exploration and showed robust activity during high-speed bouts. In object memory tasks, calcium transients (CaTs) were significantly higher during object explorations compared to spontaneous exploration in empty regions of the arena suggesting that the activity of VIP interneurons was object-modulated. Moreover, examining VIP interneurons' activity during various behavioral states revealed enhanced activity during rearing, an active exploratory behavioral state in rodents. Interestingly, CaTs were higher during grooming than active exploration periods and correlated strongly with grooming duration. In summary, these results indicate that dorsal CA1 VIP interneurons showed increased activity during active exploration and may aid in encoding episodic-like memory.

P2-F-154: *Ketamine and psilocybin differentially impact top-down predictions during the mismatch negativity*

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Both ketamine and psilocybin have demonstrated clinical value in mood and cognitive flexibility for patients with treatment resistant depression. Predicting the clinical efficacy of these pharmacological agents though, remains difficult as little is understood of their effect on neural processes. By

combining computational modelling with electroencephalography (EEG), we examine the pharmacological modulation of sensory learning in the context of the auditory mismatch negativity (MMN) component, a neural signature of surprise that has been consistently shown to be reduced under psychotomimetic interventions. Under a Bayesian framework, the brain acts as a predictive organ capable of continuously making predictions about external states in the environment and updating those predictions in response to surprising stimuli or prediction errors (PEs). We analyzed previously acquired EEG data (cf. (Schmidt et al., 2012)) and modelled single-trial EEG data using a Hierarchical Gaussian model (Mathys et al., 2014). Using a placebo-controlled within-subject crossover design, healthy subjects were administered either s-ketamine or psilocybin (ketamine group: N=20, psilocybin group: N=16) and presented with auditory roving paradigm of pure sinusoidal tones. Relative to placebo, ketamine administration led to a significantly larger reduction in the effect of belief precision from 234 to 289 ms peaking at 281 ms in the frontal central channels (peak: T (1,18) = 5.00 , p_FWE < 0.001, sensor: FCz). No significant effect was observed in the psilocybin group. This suggests that in contrast to serotonergic modulation via psilocybin, NMDAR-antagonism following ketamine administration reduces the expression of top-down belief precision in anticipation of tone regularities.

P2-F-155: *Regulation of memory by the actin-binding protein cofilin*

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Impaired social behavior is a debilitating symptom of many neurodevelopmental and psychiatric disorders, but the mechanisms underlying social behavior are poorly understood. We have shown that p-21 activated kinase (PAK) signaling in the perforant pathway is necessary and sufficient for social recognition memory in mice. However, the mechanisms by which PAKs exert these effects remain unknown. We hypothesize that PAKs act through the actin depolymerization factor, cofilin, and that cofilin-dependent actin regulation within the perforant pathway regulates social memory. Altering cofilin expression may provide a target to ameliorate impairments as cofilin-mediated actin remodeling has been demonstrated as critical for the formation and modification of dendritic spines and synaptic plasticity, the cellular correlate of learning and memory. To test this, we have generated novel transgenic mice that allow us to reversibly manipulate the expression of wildtype cofilin (cofilin-WT-GFP) or a mutant inactive form (cofilin-S3D-GFP). We have shown that these transgenes are selectively expressed in brain regions implicated in social behavior. In addition, rod-like structures are visible within neuronal cell bodies and dendrites of cofilin-WT-GFP mice. These structures are believed to be cofilin-actin aggregates associated with various brain diseases. Cofilin-WT-GFP mice also

displayed some memory impairments during testing but exhibit otherwise normal behavior. This research addresses the link between cofilin-mediated actin regulation and memory function.

P2-F-156: *Automated classification of object interaction in a rat novelty recognition task*

Timothy Onofrychuk[1], Ilne Barnard[1], Aaron Toderash[1], Vyom Patel[1], John Howland[1]

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Open-source tools created for behavioural analysis hold great potential to increase the reproducibility of behavioural data in basic research. Object interaction is a common behavioural measure used to assess cognition in rodents; however, variability in manual scoring and imprecise region of interest (ROI)-based scoring limit the reliability of observed interaction times. Here, we compared stopwatch and ROI-based scoring to an open source-based analysis pipeline using a simple three-object novelty recognition task. In this task, rats are allowed to explore three objects for five minutes, then after a one-minute delay, they are placed back into the arena with two of the original objects and a novel object for an additional five minutes of exploration. To quantify object interaction, we first generated motion tracking data using DeepLabCut, a commonly used pose-estimation package, then we quantified object interaction using Simple Behavioural Analysis (SimBA), a supervised machine learning-based method for behavioural classification. SimBA accurately predicted object interaction with 94.5% +/- 2.3% (mean +/- SEM) accuracy. We found that total interaction time was significantly different between all scoring methods (all $P < 0.001$); however, time spent at the novel object relative to total exploration was highly correlated between stopwatch and machine-based scoring ($r = 0.96$-0.99), but less so with ROI-based scoring ($r = 0.63$-0.83). This work demonstrates the performance and promise of open-source tools for automated behavioural analysis.

P2-F-157: *The impact of maternal Cannabis exposure during pregnancy on attentional processes and impulsivity of adult rat offspring.*

Ilne Barnard[1], Faith Austin-Scott[1], Spencer Orvold[1], Sarah Baccetto[1], Ashton Heidt[1], Tallan Black[1], Timothy Onofrychuk[1], Robert Laprairie[1], John Howland[1]

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Human population studies report increased learning disorder prevalence, inattention, and impulsivity in children after maternal Cannabis exposure (MCE). The major constituents of Cannabis, Δ9 tetrahydrocannabinol (THC, psychoactive) and cannabidiol (CBD, non-psychoactive), readily cross the placental barrier into the fetal bloodstream. We used a translational Sprague-Dawley rat model to examine the effects of repeated Cannabis smoke exposure (two strains: Mohawk, high-THC; Treasure

Island: high-CBD), or injected Δ9-THC (3.0mg/kg; i.p), or CBD (10.0mg/kg; i.p.), during gestational days 6 through 20. Male (n= 26) and female (n= 24) adult offspring completed a well-established, automated five-choice serial-reaction time task (5CH) to measure attention, impulsivity, and response latencies. The frequency of days it took to reach criterion on each stage of 5CH were not significantly different between treatment groups or sex. Baseline attentional performance and impulsivity were also not significantly different between treatment groups or sex. Attentional performance and impulsivity were equally impaired in all treatment groups following a shorter stimulus duration of 0.25 s compared to 0.50 s. Ongoing experiments will examine other attentional challenges and increase the sample size. We hypothesize that MCE may impact attentional performance under increasingly difficult challenges. Ultimately, these findings further our understanding of how Cannabis use during pregnancy may affect attention and impulsivity in offspring.

P2-F-158: *Intranasally administered zinc-sulfate impairs novel-odour discrimination in male Golden hamsters*

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Our group previously showed that male Golden hamsters can accurately discriminate between novel and familiar odour cues in our spontaneous behavioral paradigm (novel-odour discrimination). To the best of our knowledge, we are the first group to demonstrate that hamsters can discriminate between non-biologically significant odour cues such as herbs and spices. Briefly, hamsters are first allowed to explore two identical copies of an odour (A, A) in a square testing arena. Next, the animal is removed from the arena, and one of the odours is swapped with an identical, "familiar" copy (A for A'), and the other for a novel odour (A for B). The test animal is reintroduced to the arena, and allowed to explore either (A'), or (B). Hamsters generally spend more time exploring the novel, rather than the now familiar odour cue. Recently, we have demonstrated that intranasal administration of zinc-sulfate (5% weight per volume of distilled water) two days prior to testing impairs the ability of male Golden hamsters to discriminate between non-biologically significant odour cues, which is indicated by animals spending comparable amounts of time with both novel and familiar odours. While our initial data is promising, hamsters do not display as robust discrimination seen with rats in the same paradigm and further work is needed to improve the number of animals who reach inclusion criterion for analysis.

P2-F-159: *A role for the core and shell sub-regions of the rat nucleus accumbens in the odour span task*

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The nucleus accumbens (NAc) contributes to locomotion, reward-based learning, and addiction-related behaviours. It has been postulated that the NAc is also involved in working memory, although this idea has been met with conflicting evidence from behavioural studies. To resolve this conflicting literature, we assessed the effects of reversible inactivation of the NAc core and shell sub-regions on performance in the odour span task (OST). The OST is a test of olfactory working memory capacity that involves the incrementing presentation of odours. Rats must select a novel odour using a non-matching to sample rule, with the number of stimuli increasing after each successful selection of the novel odour. In this study, we cannulated NAc core (n=4) and shell (n+2) of male Long Evans rats. To temporarily inactivate the core or shell, we infused muscimol/baclofen (m+b) or saline, and performed a sham infusion as a control. We found that m+b infusion, but not saline or sham infusion, impaired the average span capacity (1.72 odours vs., 8.14 and 6.92 odours respectively). Additionally, we found that m+b, but not saline or sham infusion, altered the average latency to approach stimuli (6.26s vs., 10.43s and 12.40s respectively). This study provides preliminary evidence for a significant role of the NAc in the OST. Future experimentation will need to be conducted to increase statistical power in determining any differential contributions, or lack thereof, from core and shell sub-regions.

2G. Novel Methods and Technology Development

P2-G-160: *Dynamo: An open-source tool for reconstructing, tracking, and quantifying the structural dynamics of neurons*

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Brain neurons exhibit tremendous structural plasticity during growth of dendritic and axonal arbors in early brain circuit formation, followed by experience-driven structural plasticity throughout life. Advances in fluorescence-based labeling and in vivo rapid time-lapse imaging now allow capture of these dynamic structural changes within intact and awake animals. However, the resulting large 4D data sets are challenging to quantify due to time-consuming tracking of minute structural changes throughout complex neuronal morphologies across time-series of 3D image stacks. Here, we present Dynamo: an open-source Python application that enables dynamic morphometrics, the quantitative analysis of morphological changes over time, by streamlining arbor reconstruction, registration of structures across time, and quantitative analyses of growth behavior. Dynamo yields rich

characterization of neural structural changes associated with growth and plasticity necessary for determining how rapid growth events culminate into long-term patterning, linking structural and functional plasticity, and for identifying underlying molecular mechanisms. The open-source nature and rational design of the Dynamo code allows user-development of custom analytics and visualizations tools for highly flexible application of Dynamo to novel research questions.

P2-G-161: *Phosphodiesterase inhibitors as new therapies to prevent opioid-induced respiratory depression*

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Opioids are used extensively as analgesics but their side effects, such as respiratory depression, limit their effective use. Binding of opioid drugs, such as fentanyl, to their cognate μ-opioid receptor, leads to decreased cyclic adenosine monophosphate (cAMP) level and neuronal inhibition. Phosphodiesterases (PDEs) are enzymes that break down cAMP and reduce its level. Inhibition of PDEs increases cAMP levels and may reduce neuronal inhibition by μ-opioid receptors. We aim to determine whether PDE inhibitors, especially PDE-4 which is involved in opioid inhibition, may prevent respiratory depression by opioid drugs. In 7 days post-fertilization larval zebrafish, we assessed respiratory depression by fentanyl by quantifying mandible and fin movements (Zaig et al., 2021, eLife). Three treatment groups were assessed: the opioid analgesic fentanyl (8 μM), the PDE-4 inhibitor roflumilast (200 μM) and a combination of fentanyl and roflumilast. Roflumilast significantly prevented respiratory depression induced by fentanyl, when compared to fentanyl alone ($p=0.005$). Using our validated zebrafish model, we aim to test a large number of PDE inhibitors to identify effective preventive therapies. We also aim to determine whether PDE inhibition blocks the analgesic properties of fentanyl. New drugs with the ability to prevent or reverse the effects of fentanyl are critical to develop pain killers without side effects, but also to identify new opioid overdose antidotes without the risks of re-narcotization or withdrawal.

P2-G-162: *Automated assessment of chronic social isolation-induced behavior deficits using machine learning.*

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The continued lockdown and self-quarantine measures during the COVID-19 pandemic have drastically and chronically restricted our in-person and proximal social interactions. How this

prolonged social isolation will impact human health and behavior remains unclear. A more detailed analysis of behavioral dynamics to extract richer representations of social behavior is required. Computer vision has seen exponential growth and could be applied to behavior analysis leading to automated clustering of social behaviors and potentially uncovering new pathological behavioral patterns. In this study, we use machine learning methods to investigate the social behaviors of mice after seven weeks of chronic social isolation compared to that of the group-housed mice. We developed a pipeline to automate the classification of distinct social behaviors in the socially isolated and group-housed mice using a combination of unsupervised and supervised machine learning approaches. Specifically, we first use convolutional autoencoders to produce a low-dimensional continuous representation of behavior videos. We then use an autoregressive hidden Markov model to segment videos into discrete behavior states. Another unsupervised model (TW-FINCH) was used to group semantically and temporally consistent frames of the video. The resulting video clips were then observed and evaluated by a group of raters and finally created a ground truth dataset with consensus behavior class labels. Finally, an end-to-end transformer model was trained to predict behavior classes from social interaction videos. We find that this method can significantly improve the speed and precision of behavioral clustering, which lays the groundwork for characterizing behavioral abnormalities induced by social isolation.

P2-G-163: *Discovery of new pain therapies by targeting voltage-gated calcium channels in larval zebrafish*

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Opioids are the predominant analgesic drugs but may have limited effectiveness due to their addictive properties and abuse liability that can lead to lethal respiratory depression with overdose. The current challenges in drug discovery for pain therapies are to discover a potential drug with analgesic function without respiratory depression. Voltage-gated calcium channels are required for many nervous system functions, and their dysfunction can give rise to pathophysiological conditions such as pain. Considering their role in pain, we aim to discover new molecular targets and calcium channel modulators to alleviate nociception using our drug discovery platform in larval zebrafish. Zebrafish have the advantage of high production of embryos and high genetic homology with humans. To measure nociception, we exposed larval zebrafish to the nociceptive stimulus formalin which elicits a behavioral escape response. We also tested the respiratory depressant effects of drugs. We identify 16 calcium channel inhibitors that may have the potential to reduce the nociceptive response to formalin and will test the analgesic properties of these calcium channel inhibitors. We will also determine whether calcium channel subunits β, γ, δ, and α2 may be valid molecular targets for new

pain killers, by knocking out these subunits using targeted mutagenesis with CRISPR-cas9. Overall, we aim to determine whether calcium channels may constitute new molecular targets that can be modulated by drugs to reduce pain without the respiratory side effects of commonly used opioid pain killers.

P2-G-164: *Computational Microscopy for Implementing SLAP2 Functional Imaging*

Jun Shen Fung[1], John Price[1], Peter Hogg[1], Tristan Dellazizzo Toth[1], Kurt Haas[2]

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SLAP2 two-photon microscopy allows in vivo imaging of 3D brain volumes with subcellular resolution at millisecond sampling rates. Our goal is to use SLAP2 for sampling fluorescent biosensors for activity across somas and complete dendritic arbors of individual brain neurons to track sensory stimuli-evoked synaptic and action potential signalling. By combining imaging of fast neural activity with slower morphological changes, our experiments are designed to link functional and structural plasticity. To take full advantage of the speed of SLAP2 we have developed a computational microscopy software pipeline for application during experiments. We employ computer vision based machine learning software for rapid neuron identification and segmentation, to direct automated assignment of regions of interest (ROIs) for fast activity sampling. Repeated application of these machine learning software tools throughout experiments allows continuous detection of changes in neuronal structures due to growth plasticity or image drift and accommodation of ROIs.

P2-G-165: *Optimizing viral delivery and light illumination techniques for large-scale optogenetics in the primate brain*

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By combining light-sensitive proteins with intracranial light delivery, optogenetics offers unprecedented, cell-type specific control over neuronal activity. The technique has become the dominant approach for studying neural circuits in small animal models such as mice and flies. Unfortunately, optogenetics has so far failed to have a major impact on research using larger animals more similar to humans, such as macaque monkeys, undermining its translational potential for human patients. We conducted a world-wide Open Science initiative to identify the challenges remaining to be solved in primate optogenetics (Tremblay et al. Neuron, 2020). We identified the sheer size of the macaque monkey brain, which is 200 times bigger than the mouse brain, as well as its

immune system, as the main challenges for both gene expression and light delivery. Our multidisciplinary team is developing and optimizing three new technologies to address these issues : 1) large-scale, safe delivery of ultra-sensitive opsins using gene therapy techniques; 2) chronically-implantable, ultra-thin, flexible, biocompatible LED arrays; and 3) implantable, battery-powered LED drivers for wireless control during unrestrained, naturalistic behavior. This approach will allow precise control of large volumes of the primate brain with cell-type specificity and millisecond resolution in monkeys free of physical restraint, thus permitting causal dissection of the neural circuits mediating natural behavior relevant for understanding and treating human brain disorders. This technology platform could be directly applied as a cell-type-specific optogenetic therapy for humans suffering from neurological disorders that affect specific neural populations, such as focal epilepsy.

P2-G-166: *FASTMAP: open-source flexible atlas segmentation tool for multi-area processing of biological images*

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To better understand complex systems, such as the brain, studying the interactions between multiple brain regions is imperative. Such experiments often require delineation of multiple brain regions on microscopic images based on pre-existing brain atlases. Experiments examining the relationships of multiple regions across the brain have traditionally relied on manual plotting of regions. This process is very intensive and becomes untenable with a large number of regions of interest. To reduce the amount of time required to process multi-region datasets, several tools for atlas registration have been developed; however, these tools are often inflexible to tissue type, only supportive of a limited number of atlases and orientation, require considerable computation expertise, or are only compatible with certain types of microscopy. To address the need for a simple yet extensible atlas registration tool we have developed FASTMAP, a flexible atlas segmentation tool for multi-area processing. We demonstrate its ability to register images efficiently and flexibly to custom mouse brain atlas plates, to detect differences in the regional numbers of labels of interest, and to conduct densitometry analyses. This open-source and user-friendly tool will facilitate the atlas registration of diverse tissue types, unconventional atlas organizations, and a variety of tissue preparations.

P2-G-167: *Principles of Visual Cortex Connectivity*

Christina Chou[1], Kiminou Boukoulou[1], Tasha Liang[1], Connie Guo[1], Per Jesper Sjöström[1]

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Neuronal connectivity is fundamental to information processing, e.g., primary visual cortex (V1) layer 2/3 (L2/3) pyramidal cells (PCs) that share functional preference connect more frequently. To study local connectivity, multiple patch clamp is the state-of-the-art technique. However, multiple patch is slow and challenging, so cortical connectivity remains poorly explored. Therefore, we created a high-throughput optogenetic method, Two-photon Connectivity Mapping (TCM). To target V1 PCs, we injected AAV9-CAG-DIO-STChroME-P2A-mRuby in P1 Emx1-Cre mice. In P19-P25 acute slices, 1040-nm Ti:Sa laser spiral-scans drove tagged V1 PCs with single-cell and millisecond resolution. Laser-evoked EPSPs were recorded in PCs, basket cells (BCs), or Martinotti cells (MCs), classified by mDlx tag, morphology, and spike pattern. We mapped dozens to hundreds of inputs, hundreds of microns away, across all cortical layers. Within 100 µm, L5 PC-PC (17/196 = 9%; 0.34 ± 0.09 mV, n = 6 cells) and PC-BC connectivity (65/176 = 37%; 1.74 ± 0.24 mV, n = 5 cells) qualitatively matched paired recordings (7%; 0.87 ± 0.09 mV, n = 162 resp.; 100/299 = 33%; 2.10 ± 0.29 mV, n = 100), thus validating TCM. L2/3 BCs received stronger local PC input (54/233 = 23%; 1.13 ± 0.19 mV, n = 6 cells) than did L2/3 PCs (25/191 = 13%; 0.51 ± 0.12 mV, n = 5 cells), which may ensure stability. Expectedly, we could verify the canonical circuit, but surprisingly, BCs did not follow this rule. In conclusion, TCM enables large-scale connectivity mapping to reveal the principles of local visual cortex connectivity.

P2-G-168: *A Drosophila CNS organ culture to study retinoid-based transcriptional regulation*

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Retinoic acid is the active metabolite of Vitamin A and is important for nervous system development, regeneration and cognition in both vertebrate and invertebrates. Retinoic acid signaling has recently been implicated in the evolution of the mammalian prefrontal cortex, highlighting the importance of studying retinoid signaling in different species. Retinoic acid binds to two nuclear receptors, the retinoic acid receptor (RAR) and the retinoid X receptor (RXR), which both act as ligand-activated transcription factors and are conserved between vertebrates and invertebrates. However, very little is known about ligand activity and transcriptional regulation of invertebrate retinoid receptors, particularly in the context of nervous system development and function. In order to quantitatively interrogate ligand-mediated transcriptional activity, we generated a novel ligand sensor system based on the RXR from the mollusc, Lymnaea stagnalis, and generated stable Drosophila ligand sensor lines. This sensor system reports the activity of RXR activity through quantifiable changes in fluorescence reporter expression in the nervous system of living larvae and responds to retinoic acid, revealing conserved ligand binding properties between vertebrates and invertebrates. This sensor system will facilitate the study of the ligand-binding and transcriptional properties of invertebrate retinoid receptors in the context of a live nervous system and provide insights into the evolution of retinoid signaling.

P2-G-169: *An inexpensive open source micromanipulator*

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Open source technologies such as 3-D printing have been increasingly applied to the biological sciences, including neurosciences. Here, we have created an open source and versatile micromanipulator with haptics and form factor familiar to electrophysiologists. The total cost of fabrication is about $600 CAD using easily available and relatively inexpensive parts. The system is controlled by an Arduino MEGA, programmed in C++, and includes rotary optical encoders and a novel printed circuit board to control stepper motor driven linear translators. The performance of the device is good, having low noise and low drift; however kinetic performance does not equal a commercial micromanipulator as the inexpensive linear translators exhibit approximately 5µm of backlash. Therefore, the micromanipulator presented here is suitable for all but the most demanding micropositioning applications.

P2-G-170: *Studying brain activity in sleep using mobile EEG and mathematical models of corticothalamic networks*

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Neural field models are used to model brain activity across easily observable macroscopic spatial scales. In this work we use the neural field model by Robinson et al. to study corticothalamically-driven activity patterns in electroencephalography (EEG) data. The model describes an analytic power spectrum, derived from its field equations, the shape of which is defined by a series of gain (G) parameters, representing connection strengths between cortical and thalamic neural populations. The model also includes a dimensionally-reduced space with parameters x, y, and z representing cortical, corticothalamic, and thalamic activity. We used this model to study the physiology of sleep state transitions, using openly available EEG data from two sources: 1) The EDF-Extended Sleep Dataset, consisting of 197 recordings, and 2) Dreem Open Dataset, consisting of 71 recordings using the Dreem2 sleep EEG headset. Power spectral densities within 30s moving windows were calculated from these datasets using Welch's method, and the Robinson model was fitted to these spectra using an MCMC method. We observe that the fitted and empirical power spectra include similar peaks, characteristic of the corresponding canonical sleep stages. Further comparison of the model parameters and the xyz space demonstrated significantly different average parameters across sleep stages. This work demonstrates the feasibility of studying brain activity during sleep via new mobile

EEG technology, through the lens of a mathematical theory of sleep EEG dynamics in the corticothalamic system.

P2-G-171: *Evaluating glial cell response to functional microelectrode implants in vitro*

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The goal of this project is to develop a systematic approach to evaluating cell reactivity to implanted neural interface devices. Insertion of functional microwire implants designed to interface with nervous tissue (ie. intraspinal microstimulation) elicits an inflammatory response that includes gliosis, cell death, and glial scar formation that can exacerbate injury and prevent healthy recovery of affected tissue. Central to the inflammatory response are glia - whose functions include surveillance and defense of the central nervous system. Two-dimensional cell cultures are a reductionist means of assessing glial reactivity to chemical and biological stimuli, and three-dimensional cell cultures offer a more complex and appropriate physiological environment to evaluate stimuli as compared to a planar substrate. Methacrylated hyaluronic acid (HAMA) hydrogels offer a robust and reproducible 3D scaffold for in vitro culture of primary glia, and enable modeling of different injuries while reducing the ethical footprint relative to in vivo testing. We developed a HAMA cell culture tailored to evaluating glial reactivity to electrode wires and electrical stimulation. Images and cytokine secretion profiles assessing mouse glial response to embedded 75 µm diameter Platinum/Iridium electrodes suggest localized responses at the electrode-culture interface, and support published in vivo results. Using 2D and 3D cell culture systems as platforms for testing biocompatibility of different design iterations of wires will allow for improvements in implant safety and longevity.

2H. History, Teaching, Public Awareness and Societal Impacts in Neuroscience

P2-H-172: *The Lack of Resources and Research Available to young adults with glioblastoma*

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Background: Glioblastoma (GBM) is an extremely aggressive, highly fatal and the most common human primary malignant brain tumour in adults. GBM among the young adult population (age 18-39) is rare. Diagnosis, molecular genetics, prognosis, treatment effectiveness and overall course of

disease among young adults has different outcomes than in the older adult population. Although GBM affects young adults to a lesser extent than older adults, young adults are still impacted by GBM. However, there are fewer resources and information available and research studies conducted on young adult GBM patients. Methods: Provide a general survey and interview young adult GBM patients (ages 18-39) at Princess Margaret. The surveys and interviews will determine individual patient needs, wants, challenges, knowledge about course of disease and desired changes in order to create tools/platforms that cater to the individual wants and needs of patients. Goal: Our project aims to engage with the community of young adults with GBM and determine individual patient needs in terms of education, access to information and support, challenges in access to resources, and desired changes in health care. Impact: We can create tools/platforms that cater to the needs of young adult GBM patients. These tools will educate patients on resources available to them, tests and procedures that are necessary and supported by evidence, and the overall course of disease. These platforms will promote conversations between patients as well as between patients and clinicians. These platforms/tools will educate patients of choose wisely recommendations and implement them into practise.

P2-H-173: *How to cope with neurological problems and make it a routine*

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Division of Brain and Neurosurgery Medical services related to brain, neurosurgery and spine surgery that require surgical intervention are provided, including brain and spine malformations of brain arteries, brain and spine injuries resulting from accidents and falls, as well as congenital malformations of the brain and spinal cord and cerebral hematoma, in addition to the treatment of disc herniations through simple and complex surgical interventions. In addition to spinal stabilization operations. And now, with the development of life, especially from the existence of modern things that benefit societies, to simple and convenient solutions that suit the medical conditions of infected people with bilateral crises. Many solutions have been explained in scientific research, as they are suitable for all types and ages.

Poster Session 3: May 15, 2022

3A. Development

P3-A-1: *Investigation of the role of the β-arrestin signaling adaptors in Shh-mediated axon guidance*

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During nervous system development, axons are guided to their correct targets by attractive and repulsive guidance molecules. In the developing spinal cord, Sonic hedgehog (Shh) is secreted by the floor plate and attracts axons of commissural neurons to the ventral midline. In axon guidance, Shh binds to its receptor Boc and activates downstream effectors such as Smoothened (Smo) which then activate Src-family-kinases (SFKs), which are required for axon attraction by Shh. However, we don't know how SFKs are activated by Smo. β-arrestins 1 and 2 are adaptor proteins known for their role in G-protein coupled receptor desensitization. They also interact with and regulate Smo in canonical Shh signaling and they can interact with SFKs for intracellular signal transduction. Therefore we hypothesized that β-arrestins act downstream of Smo in Shh-mediated axon guidance and are required for SFK activation. We found that β-arrestins are expressed in commissural neurons and that Smo, β-arrestins and SFKs interact in co-immunoprecipitation experiments. Moreover, SFKs only interact with Smo in the presence of β-arrestins, suggesting that β-arrestins act as a scaffold to recruit SFKs to Smo. We show that depleting β-arrestins in commissural neurons prevents Shh-mediated axon guidance in vitro. We aim next to determine whether β-arrestins are required for Shh-mediated SFK activation and test the requirement for β-arrestins in axon guidance in vivo by analyzing β-arrestins conditional knockout mice. My project would identify β-arrestins as novel scaffold proteins for axon guidance.

P3-A-2: *Evidence against canonical sources of GABA at immature GABA/glycine co-releasing synapses of the brainstem*

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During an early developmental period, many nominally glycinergic neurons in the brainstem and spinal cord release GABA. The function of early GABAergic transmission is unknown, but is presumed to be important for circuit maturation. Although GABA released by neurons has been understood to

have as sole source the enzyme glutamic acid decarboxylase (GAD65 or GAD67), recent studies have shown that midbrain dopamine- and GABA-releasing neurons can also obtain GABA through uptake by plasma membrane transporters (GAT1 or GAT3). To determine the source of GABA in immature glycinergic terminals of the auditory brainstem, we collected tissue from rats aged postnatal day (P)0 to 29 and immunostained for GAD65, GAD67, GAT1, and GAT3, as well as for markers of glial cells and synaptic terminals. The GAD enzymes showed expected subcellular localization in the auditory brainstem, but expression of both enzymes was surprisingly low during the period of peak GABA transmission in the first postnatal week, rising only after the first week. The transporters GAT1 and GAT3, which showed peak expression at P12 and P4, were generally not associated with neuronal cell bodies. Our results suggest that immature GABA/glycine co-releasing neurons in the auditory brainstem acquire GABA through means other than the classical glutamic acid pathway.

P3-A-3: *Chronic adolescent restraint stress augments subsequent adult nicotine reinforcement in male and female sprague-dawley rats*

Briana Renda[1], Allyson Andrade[1], Isabella Wylie[1], Adiia Stone[1], Monica Antenos[1], Jennifer Murray[1]

[1]University of Guelph

Rationale: Early life stress has been linked to the development of depression and nicotine (NIC) dependence. Activation of the hypothalamic-pituitary-adrenal (HPA) axis, a major part of the stress response, may contribute to the abuse-potential of NIC, and hyperactivity of the HPA-axis has been linked to depression. This study aimed to characterize HPA-axis function after acute and chronic adolescent stress and assess adult depressive-like behaviour and NIC reinforcement after chronic adolescent stress. Method: Male and female Sprague-Dawley rats exposed to daily 1hr restraint stress (RS) throughout adolescence (P28-55) or adulthood (P70-97), were assessed on adult depressive-like behaviour (sucrose preference test) and NIC reinforcement (IV self-administration). Corticosterone (CORT) response to RS was assessed weekly during the stress period and baseline levels were assessed in adulthood. Results: Adolescent stressed males had reduced body weight after RS and showed depressive-like behaviour in adulthood. Chronic adolescent RS increased adult NIC consumption in both sexes, and females consumed more nicotine than males and persisted more in NIC-seeking when nicotine was withheld. Adolescent RS did not alter adult baseline CORT levels in either sex, though females had higher baseline CORT than males. Conclusions: Adolescent stress is a risk factor for depressive-like behaviour in males and NIC use in both sexes. Females are more vulnerable to increased adult NIC use regardless of stress exposure, emphasizing the need to consider sex when developing novel treatment options.

P3-A-4: *Investigating reciprocal interactions between microglia and neural precursors during cortical development using human pluripotent stem cell-derived 2D and 3D cultures*

Afrin Bhattacharya[1], Ai Tian[1], Jeremy Toma[1], Julien Muffat[1], Yun Li[1]

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The human cerebral cortex is the anatomical basis for our unique cognitive abilities. Proper cortical development entails the establishment of an appropriately sized neural precursor (NP) pool through tight regulation of NP proliferation and subsequent differentiation into neurons and glia. Emerging evidence has delineated an essential role for microglia, the immune cells of the brain, in regulating NP biology in health and disease. However, current knowledge of these neuro-microglial interactions is largely restricted to rodent models that have divergent NP properties compared to humans. To investigate the contribution of microglia in the human NP niche, we have set up an in vitro human pluripotent stem cell (hPSC)-derived co-culture system to model the interactions between human microglia and NPs, in 2D neural cultures and 3D cortical organoids. Using these complementary co-culture models, we have identified a cell non-autonomous role of hPSC-derived microglia in promoting NP proliferation. The underlying molecular mechanism is being investigated using a lentivirus-based knockout screening methodology targeting candidate microglia-secreted growth factors. Our results also suggest that NPs can reciprocally regulate microglia abundance via production of Colony Stimulating Factor-1, a factor critical for microglia survival and proliferation. These findings support a view of cortical expansion involving co-regulation between human microglia and NPs by means of cooperative exchange of growth factors.

P3-A-5: *Investigating the role of adaptor protein ShcD in neuronal proliferation and differentiation*

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Shc family adaptors mediate signals that link activated receptors to intracellular pathways. Although all four Shc proteins (ShcA-D) are expressed in the brain, their abundance varies according to cell type and development. The least characterized member, ShcD, is robustly expressed in both developing and mature nervous system, but its contributions to neural processes and their associated molecular mechanisms remain to be studied in detail. Here, we used human induced pluripotent stem cell (iPSC) differentiated as neural precursor cells (NPCs) or mature neurons combined with a ShcD knockout (KO) mouse model to investigate the role of ShcD during early stages of neuron development. First, using BrdU assay and calcium imaging, we found that iPSC-derived NPCs overexpressing ShcD have slower proliferation and altered intracellular Ca+ levels. In addition, we observed that iPSC-derived

NPCs differentiated as cortical-like neurons present premature neural differentiation, suggesting that ShcD may influence normal neuron maturation. We next asked whether absence of ShcD might affect adult neurogenesis in the mouse dentate gyrus. Interestingly, we measured an increased number of Sox2+ cells in ShcD KO mice compared to WT; however, further characterization also revealed a decreased proportion of Ki67+ to Sox2+ cells--a result that is consistent with our finding of reduced proliferation in iPSC-NPCs overexpressing ShcD. Overall, our results from loss and gain of function models suggest that ShcD may play a critical role in early neural development and potentially adult neurogenesis.

P3-A-6: *Assessment of vascularization and neurogenesis in an iPSC-derived 16p11.2 deletion organoid model*

Nicole Blakeley[1], Baptiste Lacoste[1]

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This project will expand upon Lacoste lab findings to better understand the effect of the 16p11.2 deletion (16pDel) specific to endothelial cells (EC) on angiogenesis and neural development by using Human-induced-Pluripotent-Stem-Cells and microfluidic plates, and creation of vascularized cerebral organoids. HiPSCs with 16pDel and non-isogenic control lines were differentiated into human induced-ECs. HiECs underwent positive selection after which cell identity was confirmed using immunocytochemistry. A Matrigel-based network-formation assay is used to quantify network length and sprouting, comparing control and 16pDel lines. Angiogenic activity of 16pDel and control hiECs will be compared using Microfluidic 3-Lane OrganoPlate. Vascular tube formed in the perfusable channel, sprouts through a collagen channel towards angiogenic factors. Sprouts are quantified for length, diameter, and branching. The microfluidic Graft OrganoPlate will be used to embed a cerebral organoid in growing vascular networks using 16pDel or control hiECs. Creating vascularized organoids which will then be characterized using immunohistochemistry and transcriptomics. Complexity of vascular incorporation into cerebral organoids will be investigated. Neuronal, vascular and glial cell types identified in the control versus 16pDel organoids will be compared at select time points in order to detect neurodevelopmental delays resulting from defective vascularization as seen in 16pDel mice. Early timepoints will focus on the presence of precursor cells and later timepoints will focus on differences in neuronal layering. Overall, this will further the understanding of the altered function of ECs associated with the 16pDel and its neurodevelopmental consequences.

P3-A-7: *Pten controls the timing of photoreceptor development in part through its regulation of glycolytic flux*

Joseph Hanna[1], Yacine Touahri[2], Luke Ajay David[3], Edwin van Oosten[3], Isabelle Aubert[3], Robert Screaton[1], Carol Schuurmans[2]

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Sight begins when photosensitive retinal neurons, the rod and cone photoreceptors, detect and convert light to electrical signals that are propagated via retinal interneurons to ganglion cells, and onto visual processing centers in the brain. During development, rods and cones are derived from multipotent retinal progenitor cells (RPCs) that give rise to all retinal cells in a defined temporal sequence. Both intrinsic and extrinsic cues influence RPC fate selection. Here we investigated the role of PTEN, a lipid and protein phosphatase that negatively regulates mTORC1 and AKT signal transduction cascades, in biasing RPC fate selection. Strikingly, in RPC-specific Pten conditional knock-outs (cKO), premature rod birth and accelerated outer segment maturation was observed. Transcriptomic analyses identified differentially expressed genes (DEG) in three gene ontology (GO) categories: (1) synapse/dendrite/axon formation and function, (2) metabolic processes, and (3) neural development/differentiation. Further data mining revealed upregulation of glycolytic genes (Ldhb, Hk2, GPi, Pfkl, Aldoa, Pgk1, Pkm2, Eno1, Pgam1). Glycolytic flux was indeed elevated in Pten RPC cKO cells using a Seahorse to quantify extracellular acidification rates (ECAR) as a proxy measure. 2-deoxy-d-glucose (2DG), a glycolytic inhibitor, reduced RPC proliferation and delayed rod and cone marker expression in vitro, while administration of 2DG in vivo, between P0-P7, blocked the precocious maturation of rod outer segments in Pten RPC-cKOs. Glycolysis is thus a critical driver of photoreceptor development.

P3-A-8: *Dopamine synaptogenesis in a mouse model of autism spectrum disorder*

Sarah Martin[1], Valentine Greffion[1], Jean-Francois Poulin[1]

[1]McGill University

Autism Spectrum disorder (ASD) is a diverse neurodevelopmental condition with certain behaviours that are common across the spectrum, such as challenges with social interactions and repetitive behaviours. Abnormal formation of dopamine (DA) circuits is hypothesized to underlie some aspects of these characteristic behaviours, and research in this area is ongoing. However, DA synaptogenesis in normal development is still poorly understood. Using intersectional genetics, we are investigating the neurobiological basis of ASD by mapping the normal development of DA circuits at critical timepoints (P0, P7, P14, P21, P28) and comparing this to a mouse model of ASD (Shank3b knock-out). We are using mice that express Cre and Flp recombinases to control the expression of synaptophysin-GFP (Syn-GFP) in DA neurons with a genetic reporter (RC::FPSiT) or a virus injection. Since synaptophysin is located on neurotransmitter vesicles, the expression of Syn-GFP allows us to

visualize DA release sites in the striatum with high-resolution microscopy. We are also currently investigating the activation of DA circuits in the ventral striatum during social behaviour using in vivo calcium imaging. We hypothesize that there is less DA synaptogenesis in the ventral striatum in Shank3b knock-out mice compared to wildtype mice, resulting in lower DA circuit activity in the ventral striatum during social interaction compared to wildtype mice. This series of experiments will provide insights on structural and functional features of DA circuits, and how they are altered in a model of ASD.

P3-A-9: *Maturation of prefrontal cortex- to nucleus accumbens synaptic connectivity across postnatal development*

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Autism spectrum disorders (ASD) are the most commonly diagnosed neurodevelopmental disorder, with more than 1% affected children across nations. ASD is defined by a range of social and communication deficits and repetitive and unusual sensory-motor behaviours. Typically, this disorder emerges during infancy and has no known cure. Converging evidence implicates the nucleus accumbens (NAc) afferent projections from prefrontal cortex (PFC) in modulating social interaction. However, nothing is known about how the maturation of this circuit might inform the development of social behaviour in healthy and pathological states. Here, we used whole cell patch clamp to characterize the synaptic maturation of spontaneous and PFC-evoked transmission in NAc medium spiny neurons in C57BL/6J mice and in the BTBR T+Itpr3tf/J strain, an idiopathic mouse model of ASD, during postnatal development. Our results showed increased spontaneous inhibition in the NAc of BTBR mice compared to C57BL/6J controls starting from infancy. Additionally, BTBR mice showed altered PFC-NAc presynaptic efficacy in infancy and adolescence. Understanding how brain maturation is affected in models of neurodevelopmental disorders will provide an important framework for the generation of novel diagnostic and therapeutic avenues for disorders such as ASD.

P3-A-10: *Investigating the role of netrin-3 during neurodevelopment*

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Netrins are secreted proteins that are essential for neural development. Studies of netrin-1 have identified roles regulating axon guidance, cell-cell and cell-matrix adhesion, myelination, synaptogenesis and synaptic plasticity, but few studies have focused on netrin-3. Netrin-1 and netrin-

3 are closely related, with ~54% amino acid sequence identity between paralogues in human and mouse. Netrin-1 and netrin-3 are both expressed by neurons in the developing and adult CNS, including in neocortex and hippocampus, with netrin-3 expression more restricted in distribution and beginning later in embryogenesis. Notably, mutations in the coding sequence of the netrin receptor neogenin in humans are associated with the development of autism spectrum disorder (ASD). Recent findings have identified de novo single nucleotide mutations in the coding sequence of human netrin-3 in three individuals with developmental intellectual disorder and features of autism. We hypothesize that these mutations disrupt netrin-3 function, alter neural development, and result in deficits in synapse function in the mature brain. Our studies aim to identify the functional significance of these mutations, address the cellular distribution of netrin-3 in the developing and adult CNS, and identify the consequences of disrupting netrin-3 function. We aim to determine how netrin-3 contributes to the establishment of functional neural networks during normal neural development and understand its potential impact on the development of ASD.

P3-A-11: *L3mbtl3 is a novel gatekeeper of neurogenic gene expression and mRNA processing during neocortical neurogenesis*

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The six neocortical neuronal layers are generated sequentially during development. Neurog2, a proneural transcription factor, is required and sufficient to specify early-born, deep-layer, and not later-born upper-layer neuronal fates, despite being expressed throughout cortical neurogenesis. Here we report that L3mbtl3, an MBT-domain protein that recruits Polycomb Repressive Complex 1 (PRC1) to genomic sites, is a novel Neurog2 interactor and regulator of cortical neurogenesis. L3mbtl3 and Neurog2 are co-expressed, along with PRC1 and PRC2 genes in neural progenitor cells (NPCs). In L3mbtl3 knock-outs (KOs), fewer upper-layer neurons are generated, while cortical NPCs expand. Transcriptomic analyses revealed a marked derepression of transcriptional repressors, including Rest, Sfmbt1, and Tle4, and an associated downregulation of glutamatergic neuronal differentiation genes in L3mbtl3 KOs. MBT domain proteins recruit PRC1 via a conserved Yy1 repressive complex, and strikingly, a gene regulatory network with Yy1 as a central hub gene is underrepresented in L3mbtl3 KOs. Nevertheless, chromatin architecture remains unaltered in L3mbtl3 KOs. Instead, L3mbtl3 overexpression in cortical NPCs suppresses mRNA export and splicing factor gene transcription, effectively suppressing neural marker protein detection, and preventing cortical NPC differentiation

and migration. L3mbtl3 is thus an essential gatekeeper of cortical neurogenesis, repressing neurogenic transcriptional repressors and mRNA processing genes.

P3-A-12: *Investigation of the role of WAVE regulatory complex in Shh-mediated axon guidance*

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During nervous system development, Sonic hedgehog (Shh) functions as a guidance cue to attract axons of spinal cord commissural neurons to the ventral midline. Shh signaling leads to remodeling of the growth cone cytoskeleton that allows the growth cone to turn. Shh-mediated attraction of commissural axons requires the receptor Boc. However, how Boc regulates cytoskeletal changes in growth cones in response to Shh remains poorly understood. Thus, we aim to elucidate the molecular mechanisms behind Boc-mediated cytoskeletal dynamics in Shh-dependent axon guidance. We used a BioID assay to screen for proteins interacting with Boc. Top hits of the screen included NCKAP1 and CYFIP2, members of the heteropentameric WAVE regulatory complex (WRC). The WRC acts downstream of Rac1 to promote actin cytoskeleton assembly. Therefore, we hypothesised that the WRC may be important for Shh-induced cytoskeleton rearrangement and growth cone turning. We first confirmed that the WRC is expressed in commissural neurons. Using co-immunoprecipitation assays, we then confirmed the interaction between Boc and the WRC and found that the Boc-WRC interaction is regulated by Shh. Moreover, we found that knockdown of NCKAP1 and CYFIP1/CYFIP2 in commissural neurons prevents attraction of axons toward a Shh gradient in vitro, indicating that NCKAP1 and CYFIP1/CYFIP2 are required for Shh-mediated axon attraction. This study will elucidate how Shh regulates cytoskeletal changes that underlie growth cone turning, contributing to understanding nervous system wiring and neurodevelopmental disorders.

P3-A-13: *Self-other processing deficits in atypical developmental trajectories of psychotic experiences*

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Self-disturbances have been reported across the psychosis continuum, however, studies of psychosis risk have not accounted for the changing levels of psychotic symptoms during adolescence. This study aimed to investigate the neural bases of self-other processing before the onset of clinical psychotic symptoms in youths belonging to developmental trajectories of psychotic experiences. 86 youths

were recruited from a sample of over 3,800 adolescents that were followed for 4 years. Three groups were determined based on validated developmental trajectories of psychotic experiences: a low-decreasing control trajectory, a decreasing trajectory and an increasing trajectory. Functional magnetic resonance imaging data was collected during self and other-related processing, and activation analyses were conducted. At age 17, the decreasing trajectory displayed more negative psychotic symptoms while the increasing trajectory displayed more positive psychotic symptoms. Both atypical trajectories displayed decreased activation of the dorsomedial prefrontal cortex, the superior temporal gyrus and the right inferior frontal gyrus. The decreasing trajectory also displayed decreased activation of the middle occipital gyrus. In conclusion, both atypical trajectories showed alterations suggesting impaired differentiation between the self and others and impaired salience attribution, similarly to what has been observed in psychosis. The decreasing trajectory displays further deficits suggesting more generalized cognitive impairments, which could explain the prevalence of negative symptoms.

P3-A-14: *Human genetics of mirror movements identifies a novel regulator of commissural axon guidance.*

Sabrina Schlienger[1], Patricia Yam[2], Nursen Balekoglu[1], Jean-Francois Michaud[3], Shirin Makihara[1], Myriam Srour[1], Frédéric Charron[2]

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Congenital mirror movements (MM) disorder is characterized by involuntary movements on one side of the body that mirror voluntary movements of the homologous body part on the opposite side. MM results from a dysfunction in motor control lateralization. We performed whole exome sequencing of seven affected members of a family with autosomal dominant MM and identified ARHGEF7, a RhoGEF known to regulate cell polarity, adhesion and migration, as a candidate MM gene. We found that Arhgef7, together with its partner Git1, binds directly to Dcc. Dcc is the receptor for Netrin-1, an axon guidance cue that attracts axons to the midline during development, promoting the midline crossing of axon tracts which is important for the lateralization of motor control. We show that Arhgef7/Git1 activates Rac1 and Cdc42 and inhibits Arf1 downstream of Netrin-1. In addition, Arhgef7 and Git1, via Arf1, mediates the Netrin-1-induced increase in cell surface Dcc at the growth cone. We demonstrate that Arhgef7 and Git1 activity are required for Netrin-1-mediated axon guidance in vitro. In vivo , mice heterozygous for Arhgef7, a model for the MM individuals that have a mutation in one allele of ARHGEF7, have defects in commissural axon trajectories in the embryonic spinal cord, consistent with impaired Netrin-1/Dcc signaling. Adult Arhgef7 het mice have increased symmetrical paw placements during skilled walking, thus displaying a MM-like phenotype. In conclusion, we have identified

mutations in ARHGEF7 that cause MM and delineated the pathogenic mechanism via which ARHGEF7 mutations cause MM.

P3-A-15: *Investigating human-specific brain development using comparative genomics and pluripotent stem cell-derived 2D/3D neural cultures*

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The massive expansion and complex folding pattern of the human brain arise from the evolution of the cerebral cortex. Specifically, changes during the proliferation and differentiation of neural stem and progenitor cells (collectively known as neural precursors or NPs), and potentially the emergence of a NP subtype, outer radial glia (oRG), result in human-specific neurodevelopmental features and intellectual abilities. Pluripotent stem cell (PSC)-derived 2D and 3D neural cultures have allowed us to study cortical development in vitro in human and other species, where fetal brains are often inaccessible. I will perform a multi-species comparison of PSC-derived neural cultures from 3 primate species, human, macaque, and marmoset, to investigate cellular and molecular mechanisms controlling species-specific cortical development. To date, I have successfully established PSCs and have derived 2D NP cultures and 3D brain organoids for all 3 species. To specifically study and mark oRG, I utilized CRISPR/Cas9 to make reporter HOPX-tdTomato PSC lines in all 3 species. Through single cell RNA-sequencing (scRNA-Seq) analysis of our in vitro human neural culture, I identified an oRG population amongst other neural cell types. oRG emerge later compared to other radial glial cells in vitro, recapitulating in vivo development. Ultimately, I will identify differentially expressed genes and gene regulatory elements between NPs from these species by RNA-Seq and assay for transposable chromatin-sequencing (ATAC-Seq) to better understand mechanisms underlying human-specific neurodevelopment.

P3-A-16: *Generation of different oligodendrocyte lineage cell states following direct reprogramming of GFAP+ astrocytes*

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Oligodendrocyte (OL) loss or dysfunction is a hallmark of many central nervous system (CNS) conditions. Direct lineage reprogramming (DLR) is a new strategy for CNS repair, where a donor cell

is converted into a target cell without a pluripotent intermediate. Here we show that astrocytes can be directly reprogrammed to different OL lineage cells in vitro using transcription factors (TFs) involved in OL fate determination. Postnatal cortical astrocytes were purified and transduced with lentiviruses containing GFAP-driven TFs. We found that ectopic expression of each of the single TFs produced different types of OL lineage cells. Ectopic expression of a TF important for late OL development resulted in the generation of MBP+ myelinating OLs (mOLs), while expression of an early OL fate determinant generated PDGFRα+ oligodendrocyte progenitor cells (OPCs). Finally, expression of a third TF, expressed throughout OL development, produced cells at various stages of the OL lineage (OPCs, newly forming OLs (nfOLs) and mOLs). Live cell imaging of the reprogramming process confirmed that reprogrammed OLs originate from S100β expressing astrocytes. Finally, single cell RNA sequencing revealed different iOL gene signatures depending on TF delivered. These findings suggest that ectopic expression of TFs in astrocytes results in the generation of OLs at different stages of maturity. These studies lay the groundwork for novel, DLR-based therapeutic strategies for diseases involving OL lineage cell loss with possibilities to tailor iOL production according to the OL type lost in disease

P3-A-17: *Premature white matter microstructure in female children with a history of concussion*

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Background: Concussions can interfere with development and influence emerging cognitive abilities. Females are more likely to have persistent problems, yet sex-specific effects of concussions on brain microstructure in childhood is not well understood. Objective: (1) Investigate differences in brain microstructure between children with and without concussion. (2) Examine relationship between altered brain microstructure and cognition. Methods: Neurite density (ND) measures from diffusion weighted MRI were examined in children (9-10 years) in the Adolescent Brain Cognitive Development Study with (n=336) and without (n=7368) concussion. (1) Multivariate regression was used to analyze relationships between concussion history, sex, and age in deep and superficial white matter, subcortical structures, and cortex. (2) Principal component analysis was performed on ND and components were examined in relation to performance on attention and processing speed tests. Results: All tissue types had higher ND with age reflecting brain maturation. (1) Females with concussion had higher ND in white matter. (2) Higher ND in superficial white matter beneath the frontal and temporal cortices was associated with lower scores of processing speed in females with concussion, and higher scores in males with concussion. Conclusion: Concussion in childhood may lead to premature white matter maturation in females and is associated with lower scores on

processing speed tests. These sex-specific effects may contribute to the enhanced vulnerability to persistent symptoms after concussion in females.

P3-A-18: *Developmental cannabis exposure effects on ventral tegmental area dopamine neuron electrophysiological properties and response to cocaine*

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Human epidemiological and preclinical animal studies indicate a connection between gestational cannabis exposure and behavioural and cognitive deficits. However, the mechanisms behind these changes are poorly understood, and animal studies have historically injected cannabis, which does not model human consumption. We investigated the impact of maternal oral cannabis consumption on ventral tegmental area (VTA) dopamine neuron activity and reward-seeking behaviour in offspring. Dams received whole cannabis extract (5 mg/kg THC) in peanut butter or peanut butter with vehicle from GD0-PD10. VTA dopamine electrophysiological properties and reward-seeking behaviour were interrogated in adolescent (P42-P46) offspring using patch clamp electrophysiology and cocaine conditioned place preference. VTA dopamine neurons of male cannabis-exposed offspring were more depolarised and had increased spontaneous firing, shorter latency to fire, and increased after-hyperpolarisation potential height. Female VTA dopamine neurons of cannabis-exposed offspring had narrower after-hyperpolarisation potentials only. No differences were apparent in either the acute locomotor effects of cocaine or the strength of the cocaine pairing in either sex. Consistent with previous injection studies, prenatal exposure to oral cannabis differently alters the firing properties of male and female VTA dopamine neurons. In contrast to previous reports of potentiation of the reinforcing properties of opioids in cannabis exposed offspring, cocaine does not produce a similar response, suggesting a drug-specific effect.

P3-A-19: *Neurog2-Ascl1 co-expression defines a novel pool of fate restricted neural progenitor cells in the developing retina*

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During development, multipotent retinal progenitor cells (RPCs) undergo identity transitions in overlapping temporal windows to give rise to the six neuronal and one glial cell type that make up the mature retina. RPCs are multipotent, and give rise to clones that contain all seven retinal cell types, with final cell fate selection being a stochastic choice. Here we identified a pool of RPCs that co-express the proneural transcription factors, Neurog2 and Ascl1. To assess how these RPCs differ, we sorted Neurog2/Ascl1 negative, single, and double+ RPCs and performed transcriptional analysis. We identified 7,145 differentially expressed genes, with double+ RPCs preferentially expressing genes involved in amacrine cells differentiation, such as Pax6, Neurod1, Neurod4. Pseudotime trajectory analysis using scRNAseq data suggests that double+ cells are early and late RPCs that are biased to differentiate into amacrine cells. To examine the fate and function of Neurog2/Ascl1 double+ RPCs in vivo, we used a novel split-Cre system, in which the N-terminus of Cre was knocked into the Neurog2 locus while the C-terminus of Cre was knocked into the Ascl1 locus. Lineage tracing using split-Cre;Rosa-zsGreen shows that Neurog2+Ascl1+ RPCs give rise almost exclusively to amacrine cells. Strikingly, ablation of Neurog2+ Ascl1+ RPCs results in a partial to complete loss of amacrine cells. In summary, Neurog2/Ascl1 co-expression defines a novel and unique population of RPCs that gives rise to amacrine cells, providing a new mode of action for how some RPCs become lineage restricted.

P3-A-20: *Exploring the combinatorial functions of the proneural genes Neurog1 and Neurog2 in neocortical neurogenesis*

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Proneural genes encode basic-helix-loop-helix transcription factors that promote neural progenitor cell (NPC) differentiation in the developing nervous system. In the embryonic neocortex, we found that the proneural gene, Neurog1, acts non-canonically as a negative regulator of early-stage neurogenesis by competitive inhibition of Neurog2. Paradoxically, Neurog1 and Neurog2 are required to specify a glutamatergic neuronal identity in the neocortex. It is possible that Neurog1 and Neurog2 have different functions, depending on whether they are expressed in the same or different NPCs. By mining scRNA-seq data from human cerebral organoids, we found that double+ NPCs exist within these organoids, with lineage trajectory analyses revealing the presence of mainly TBR2+ intermediate neuronal progenitors (INPs). We validated this in the rodent cortex by generating two new knock-in lines, Neurog1CCreKI and N2NCreKI, in which the C-and N-terminal regions of Cre were knocked-in to Neurog1 and Neurog2 loci, respectively. From crosses with a Rosa-ZsGreen reporter line, we found that Neurog1-Neurog2 co-expressing NPCs gave rise to many INPs in the early cortex, and later, gave rise to neurons throughout the deep and superficial layers of the cortical plate. Finally, to assess the functional requirement of double+ NPCs, Neurog1CCreKI;N2NCreKI mice were intercrossed with

Rosa-DTA mice, in which cell death is achieved by diphtheria toxin. In split-cre;Rosa-DTA triple transgenics, we found striking gyrification of the neocortex that we are currently analyzing and will report. In summary, Neurog1-Neurog2 co-expressing NPCs have a unique functional role in guiding neurogenesis in the developing neocortex.

3B. Neural Excitability, Synapses, and Glia: Cellular Mechanisms

P3-B-21: *Insights into the evolutionary origins of ionotropic glutamate receptor function and ligand activation from the homologues of the early diverging animal Trichoplax adhaerens.*

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NMDA, AMPA, and Kainate receptors are ligand-gated cation channels that mediate fast excitatory synaptic transmission in mammalian brain. NMDA receptors are activated by glutamate and glycine, AMPA and Kainate receptors are activated strictly by glutamate. Recently, phylogenomic studies have revealed that NMDA receptors evolved in the common ancestor of Cnidarians (e.g., jellyfish) and bilaterians and are absent in the earliest-diverging phyla of Placozoa, Porifera (sponges), and Ctenophora (comb jellies). Instead, AMPA and Kainate receptors evolved from an ancestral AMPA/Kainate/Delta/Phi (AKDF) type receptor, which is present in all animal lineages except for ctenophores. The most ancestral type of metazoan ionotropic glutamate receptors (iGluRs) are the Epsilon receptors, which like NMDA receptors can be activated by glutamate and/or glycine. To better understand the evolution of iGluRs, we are characterizing the in vitro properties of Epsilon and AKDF receptor homologues from the placozoan Trichoplax adhaerens, an animal that lacks a nervous system but is capable of directed locomotion. We show that the placozoan AKDF channel resembles NMDA and Epsilon receptors in its sensitivity to glutamate and glycine, suggesting that dual ligand sensitivity was an ancestral feature of iGluRs, and that AMPA and Kainate receptors lost glycine sensitivity as they evolved. In contrast, a Trichoplax Epsilon iGluR is activated strictly by glycine, but not glutamate. Given that glycine is a chemoattractant for Trichoplax, we hypothesize that iGluRs activated by glycine may be involved in this behavior, and that glycine was a crucial ligand for iGluRs in early animals.

P3-B-22: *Role of M1R antagonists in the regulation of mitochondrial function and membrane potential activity in human neuroblastoma cells and primary neurons*

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Impairments in mitochondrial physiology play a role in the progression of multiple degenerative conditions in diabetes, such as diabetic neuropathy. Blockade of muscarinic acetylcholine type 1 receptor (M1R) with specific/selective antagonists prevented mitochondrial dysfunction and reversed nerve degeneration in vitro and in vivo. In models of diabetic neuropathy, inhibition of M1R using pirenzepine (PZ) or muscarinic toxin 7 (MT7) induced AMP-activated protein kinase (AMPK) activity in dorsal root ganglia (DRG) and prevented distal nerve fiber loss. Therefore, we tested the hypothesis that PZ or MT7 could enhance AMPK activity and augment mitochondrial function in human neuroblastoma SH-SY5Y cells. SH-SY5Y cells were treated with PZ and MT7 in the presence or absence of inhibitors or siRNAs of AMPK. Antagonist treatment in SH-SY5Y culture increased AMPK phosphorylation and mitochondrial protein expression (OXPHOS). Mitochondrial membrane potential (MMP) was augmented in PZ treated cells. Exposure to PZ for 6h increased the MMP with earlier time points without effect. Compound C or AMPK (α1 and α2)-specific siRNA suppressed PZ- or MT7-induced elevation of mitochondrial function and MMP. Cultured DRG neurons were loaded with voltage sensor probe DiBAC4(3) to evaluate the plasma membrane potential (Vm). MT7 and PZ induced hyperpolarization thus regulating neuronal excitability. These results reveal a M1R-modulated pathway that could represent a potential therapeutic target to control AMPK activity, mitochondrial function and nerve regeneration in diabetic neuropathy. Funding: MITACs and WinSanTor Inc.

P3-B-23: *Neurosteroid modulation of α7 nicotinic acetylcholine receptors in the mouse prefrontal cortex*

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The medial prefrontal cortex (mPFC) plays an integral role in cortico-limbic circuitry. This role is supported by acetylcholine (ACh) signalling within the mPFC via its nicotinic class of receptors (nAChRs). The progesterone-derived neurosteroid 3α-hydroxy-5α pregnan-20-one (allopregnanolone; ALLO) is produced within the brain and is well-known to exert anxiolytic effects via positive allosteric modulation of GABAergic signalling. ALLO also inhibits nAChRs in reduced synaptosomal preparations. However, the mechanisms and functional impact of this inhibition are not well understood. We addressed this knowledge gap using whole-cell electrophysiology in acute brain slices made from adult mice of both sexes. Initial experiments found that ALLO inhibits the function of α7-type nAChRs located on pyramidal neurons within layer V of the mPFC, in both a time- and concentration-dependent manner. Pharmacological experiments interrogated a potential indirect mechanism for ALLO's action via the membrane progesterone receptor (mPR) and its associated regulator "progesterone receptor membrane component 1" (PGRMC1). Although agonist activation of

the mPR did not replicate ALLO's effects, blockade of PGRMC1 completely attenuated ALLO inhibition of α7 nAChR function. Similarly, blockade of protein kinase C phosphorylation activity also completely attenuated ALLO inhibition of α7 nAChR function. These findings suggest an indirect intracellular mechanism by which ALLO negatively modulates nAChR function within the mPFC, which may negatively impact ACh-dependent cognitive functions.

P3-B-24: *Modulation of electrical transmission by cAMP through a postsynaptic mechanism*

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Electrical synapses, or gap junctions, link neurons to facilitate synchronous firing. Various signalling pathways, including cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA), can modulate electrical transmission, either by impacting the connexin/innexin gap junction-pore forming subunits, or altering postsynaptic membrane properties. In the sea snail, Aplysia californica, reproduction is initiated by the bag cell neuron afterdischarge. Specifically, these electrically coupled neuroendocrine cells secrete egg-laying hormone during a synchronous and prolonged burst of action potentials. Early in the afterdischarge, cAMP is produced to trigger PKA, which prior work showed inhibits K+ channels and enhances excitability. However, the effect of this pathway on electrical coupling is unknown. To explore this, the present study employed pairs of cultured bag cell neurons subjected to whole-cell recording and treated with either the phosphodiesterase inhibitor, IBMX, or the cAMP analogue, 8-CPT-cAMP. These reagents consistently increased input resistance, coupling coefficient (assayed by the transfer of presynaptic to postsynaptic hyperpolarization), and the amplitude of electrotonic potentials (evoked by presynaptic action potentials). Notably, dual voltage-clamp showed that cAMP did not alter the junctional conductance between neurons. These data support the concept that cAMP (and perhaps PKA) augments electrical transmission by inhibiting postsynaptic membrane conductance (likely K+). Thus, cAMP may promote afterdischarge synchrony and reproductive hormone release.

P3-B-25: *Spatially Distinct Gene Expression Changes In The Cortical Midline*

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The retrosplenial cortex (RSC) participates in many higher-order cognitive functions and contains neurons with complex, conjunctive firing properties. The RSC is broadly divided into two vast subregions, the granular (RSCg) and dysgranular (RSCdg), which differ based on differences in

connectivity and coarse anatomical definitions. However, the precise organizational principles of cells comprising these regions, which give rise to a multiplicity of functions, are ill-defined. To investigate this lapse in current knowledge, we utilized spatial transcriptomic techniques to uncover the identity and spatial locations of excitatory neurons comprising the RSC. We first performed single cell RNA sequencing (scRNA-seq) to identify transcriptomically unique subpopulations. Next, we spatially registered these cell types using multiplexed fluorescent in situ hybridization (mFISH). Finally, we implemented Visium to compare how the transcriptomic profile of this region compared to the rest of the cortex. Our data uncovered 8 excitatory cell types within the RSC, many of which demonstrate spatial restriction solely to the RSC or its subregions. This runs contrary to current thought on the cortex, wherein slow graded changes in gene expression across multiple regions are expected. Through Visium analysis, we discovered that the RSC clusters out as a unique transcriptomic region of the cortex. Finally, our data demonstrates that the RSCg has highly unique layers II/III and IV as compared to the rest of the cortex - suggesting potential for unique transcriptomic profile along midline structures of the brain.

P3-B-26: *The role of astrocyte glucocorticoid receptors in stress-induced synaptic plasticity deficits*

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Glucocorticoid receptors (GRs) are key elements in the central response to stress. The assumption in most studies investigating the central effects of glucocorticoids is that this stress hormone activates neuronal receptors to elicit synaptic effects. Recent evidence challenges this idea suggesting that the effects of stress on synapses are mediated through astrocytes. Despite these data highlighting stress sensitivity in astrocytes, whether the stress-induced impairments of synaptic function occur through direct activation of GRs on astrocytes remains unknown. Thus, we aim to understand the role of astrocyte GR signalling in mediating the effects of stress on synaptic function. To accomplish this, astrocyte GRs will be genetically ablated in mice, and subsequently mice will be subjected to a swim-stress paradigm. Long-term potentiation (LTP) will be recorded from acute hippocampal brain slices. We have found that acute stress impairs hippocampal LTP, and we hypothesise that astrocyte GR contributes to these effects. As such, we are now carrying out LTP experiments in GR-flox mice injected with AAV2/5-GfaABC1-cre into the hippocampus to elucidate the role of astrocyte GR signalling in naïve and stress conditions. These data will elaborate on the role of astrocyte GR signalling in stress-induced synaptic dysfunction, further emphasizing the pivotal role of neuron-glial interactions in mediating the central effects of stress.

P3-B-27: *Conditional knockout of wild type huntingtin in mice results in impaired short and long term hippocampal synaptic plasticity*

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Huntington disease (HD) is an autosomal dominant neurodegenerative disease that results in a triad of motor, cognitive and psychiatric symptoms. Being a monogenic disorder, it is an ideal candidate for genetic therapies, which can target the root cause of HD: the mutant huntingtin (HTT) gene. However, many of these therapies in clinical trials for HD also result in lowered levels of the wild type HTT (wtHTT) protein, which has been suggested to play an important role in cellular functions that promote synapse stability and plasticity, such as axonal transport, neurotransmitter release and receptor localization. Synaptic disruption occurs early in HD and is known to precede and predict neuronal cell death. Consequences of wtHTT reduction in the adult brain remain poorly understood, and additional research at the preclinical level is required immediately to better understand the risk factors associated with HTT-lowering therapeutics. To investigate the synaptic consequences of wtHTT reduction, we used a conditional knockout (cKO) mouse model where CaMKII-AAV-Cre was injected bilaterally into the hippocampus of wtHTT floxed wild type mice at 2-4 months of age. Basal synaptic function from acute hippocampal slices was measured 1-2 months post-injection using a multielectrode array and theta-burst stimulation (TBS) was applied to CA3 to induce long-term potentiation (LTP) at Schaffer collateral synapses. Compared to controls, wtHTT cKO mice had lowered post-tetanic potentiation and LTP, as well as impaired paired-pulse facilitation. Previous results from our lab have shown that siRNA-mediated wtHTT reduction in cultured hippocampal cells results in excitatory synapse loss, indicating that wtHTT loss in the adult brain may compromise both synaptic structure and function.

P3-B-28: *Single-cell response and variability following non-invasive brain stimulation*

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Interest in probing and controlling brain activity, particularly for medical intervention, through the use of external force has a long history. In recent years, non-invasive techniques, such as transcranial electrical stimulation, have been used to influence neural oscillations, the excitability of the network, and attempting novel therapeutic approaches. Despite this, little is known about the impact of these techniques at the level of individual neurons, a task that is experimentally intractable. Further, existing models of non-invasive stimulation are often abstracted for computational efficiency, making use of mean-field approaches and simplified neuron models that do not account for morphological

differences in their frameworks. The Allen Institute has made available morphologically-accurate models of individual excitatory and inhibitory cells from mouse visual cortex. Using these models, we simulate non-invasive stimulation and investigate the physical properties that influence the response depending on the field strength. With these metrics, we investigate how temporarily structured stimuli recruit different neuron morphologies. Probing this parameter space creates an avenue to test the potential of specific targeting through non-invasive stimulation. Further, understanding the range of response offers an approach to improve existing computational models to better capture the underlying dynamics of the system and improve our understanding of the effects of non-invasive stimulation on the brain.

P3-B-29: *Functional heterogeneity of astrocytes in the CA1 hippocampus*

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Recent gene expression studies highlight astrocyte heterogeneity between and within brain regions. However, astrocyte functional heterogeneity remains poorly understood. Here, we examine multiple physiological aspects of astrocytes distinguished by their specific spatial relation to hippocampal CA1 pyramidal cell domains: astrocytes covering the perisomatic area in stratum pyramidale (SP), or the apical dendritic area in stratum radiatum (SR). Ca2+ imaging of SP and SR astrocytes in slices revealed differences in astrocyte spontaneous Ca2+ activity. SR astrocytes display greater frequency, duration, and synchronicity, but reduced amplitude, of Ca2+ events in comparison to SP astrocytes. Whole-cell recordings and confocal imaging showed a typical bushy organisation of SR astrocytes while SP astrocytes were more polarized. SR astrocytes had a larger syncytium and lower membrane resistance relative to SP astrocytes. Finally, the specific astrocyte regulation of perisomatic and dendritic inhibitory synapses was investigated using optogenetic and Gq-DREADD approaches. The amplitude of optogenetically-evoked IPSCs in pyramidal neurons were reduced by DREADD-induced astrocyte activation by 42% at dendritic inhibitory synapses from somatostatin interneurons and 39% at perisomatic inhibitory synapses from parvalbumin interneurons. This inhibition is prevented when astrocyte intracellular Ca2+ is chelated within, but not outside, the syncytium overlapping the respective inhibitory synapse territory. These findings highlight a functional heterogeneity of astrocytes in the hippocampus.

P3-B-30: *Interferon gamma regulates cortical synaptic plasticity and behavioural output*

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The immune system and the central nervous system were believed to be independent of one another, yet many immune molecules not only exist in the CNS but play an active part in modulating synaptic function. A screen of immune factors regulated by neuronal activity identified the pro-inflammatory cytokine Interferon gamma (IFNγ) as a potential regulator of neuronal function. We therefore investigated the role of IFNγ in the regulation of excitatory and inhibitory cortical synapses and behavioural differences in a knock-out rodent model. Using cortical rat neuronal dissociated cultures, we examined the effect of short-term IFNγ treatment on glutamate-mediated excitation and GABA-mediated inhibition via electrophysiology. Our data demonstrates that acute IFNγ treatment significantly alters mEPSCs and mIPSCs, at different doses (10ng/ml and 100ng/ml). To corroborate the electrophysiological changes at the synapse, we performed immunocytochemistry with IFNγ treatment on cortical pyramidal neurons to monitor receptor trafficking of GluA1 and GABA-A receptors. Our data indicates that acute IFNγ treatment alters the amount of these receptors present on synapses at 10 ng/ml and 100 ng/ml. We also investigated the behavioural consequences of the loss of IFNγ signalling in IFN receptor knockout mice. Using the light-dark box test, we found that IFNγ receptor KO mice experience higher baseline anxiety-like behaviour compared to WT mice. Altogether this data reinforces that the neuroimmune system can modulate synaptic plasticity and behaviour output, through many factors including IFNγ.

P3-B-31: *Discrepancy between NMDA receptor effects at synapse and dendrite in patient derived GRIN1 mutant mouse leads to unexpected treatment opportunity*

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GRIN1 neurodevelopmental disorder is a rare disease caused by mutations in the obligate GluN1 subunit of NMDA receptors (NMDAR). Y647S+/- mutation in the transmembrane region of GluN1 causes intellectual disability and seizures in a patient, with unknown effects on NMDAR function and synaptic integration. To determine appropriate treatment strategies, we sought to identify the nature of NMDAR deficits using transgenic mice of both sexes heterozygous for the Y647S mutation compared to littermate controls. Patch-clamp electrophysiology in prefrontal layer 5 pyramidal neurons revealed seemingly paradoxical results. Some aspects of NMDAR signaling are diminished, but others are amplified/prolonged. Electrically evoked synaptic NMDAR EPSCs are significantly smaller in Y647S mice, yet whole-cell currents evoked by bath-applied NMDA are significantly larger. This contradictory pattern is also observed on examining dendritic plateau potentials that require NMDARs for synaptic integration. The amplitude of plateau potentials is smaller in Y647S mice, but their duration is significantly and unexpectedly prolonged. We hypothesize that this pattern in Y647S

mice arises from a combination of deficient synaptic NMDARs along with an impairment in typical NMDAR recruitment of calcium-activated potassium channels to act as brakes on postsynaptic activity. Consistent with this hypothesis, a drug potentiating calcium-activated potassium channels (NS309) is successful in reducing whole-cell currents evoked pharmacologically with NMDA. NS309 also restores appropriate timing to dendritic plateau potentials in Y647S mice. These findings give insight into dynamic interactions between NMDARs and proximal ion channels and identify a new research direction for GRIN disorder treatment.

P3-B-32: *Dendritic channelopathies alter the synaptic integration of excitatory inputs in the basal dendrites of layer 5 pyramidal in a mouse model of Fragile X Syndrome*

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Fragile X syndrome (FXS) is the most frequent form of inherited intellectual disability and common known cause of autism. Defects in the processing and integration of excitatory inputs in cortical neurons likely contributes to the behavioral phenotype associated with FXS. A key function of the neocortex is to associate external sensory information with an internal representation of the world to make predictions about the future. Layer 5 (L5) pyramidal neurons integrate sensory inputs onto their basal dendrites with information from other cortical areas at their distal dendrites. Here, we aimed to uncover how L5 pyramidal neurons from Fmr1KO mice integrate synaptic inputs at the level of single spines in the basal dendrites. We used two-photon uncaging of caged glutamate to activate nearly simultaneously two clustered spines in L5 pyramidal neurons. While excitatory inputs onto spines integrate linearly before the generation of a dendritic spike in wild-type animals, surprisingly those of Fmr1KO mice summate sublinearly. Since FXS is characterized by several channelopathies in pyramidal cells, we are currently investigating the role of calcium-activated potassium channels in explaining the observed integration defects using genetic manipulations and numerical simulations. Taken together, the results from these experiments will help uncover the role of ion channels in excitatory input integration and identify novel targets for the design of specific drugs to successfully treat FXS. This work was funded by the CIHR, as well as FRQS and QART postdoctoral fellowships to DEM.

P3-B-33: *Developmental changes in the intrinsic properties and synaptic function of pyramidal neurons in the auditory cortex of Cntnap2 KO rats.*

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Disruptions in the Cntnap2 gene are known to cause language impairments and symptoms associated with autism spectrum disorder (ASD) in humans. Importantly, knocking out this gene in rodents results in ASD-like symptoms that involve auditory processing deficits. This study used in vitro electrophysiology to examine developmental alterations in auditory cortex pyramidal neurons of Cntnap2-/- rats, hypothesizing that CNTNAP2 is essential for maintaining intrinsic neuronal properties and synaptic wiring in the developing auditory cortex. Whole-cell patch-clamp recordings were conducted in wildtype and Cntnap2-/- littermates at 3 postnatal age ranges (P8-12, P18-21, and P70-90). Consistent changes across age were seen in all measures of intrinsic membrane properties and spontaneous synaptic input. Intrinsic cell properties such as action potential half widths, rheobase, and action-potential firing frequencies were different between wildtype and Cntnap2-/- rats predominantly during the juvenile stage (P18-21), whereas adult Cntnap2-/- rats showed higher spontaneous (sEPSC) and mini excitatory post-synaptic currents (mEPSC) frequencies, with lower sEPSC amplitudes. These results indicate that intrinsic cell properties are altered in Cntnap2-/- during the juvenile age, leading to a hyperexcitable phenotype during this stage of synaptic remodeling and refinement. While intrinsic properties eventually normalize by reaching adulthood, changes in synaptic input seem to manifest in the adult age and are presumably responsible for the hyperreactive behavioral phenotype.

P3-B-34: *The M3 muscarinic receptor influences muscarinic modulation of pyramidal neuron excitability within layer VI of the mouse medial prefrontal cortex*

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Acetylcholine (ACh) modulates the excitability of neurons within the medial prefrontal cortex (mPFC) to support normal cognitive functions. ACh fulfills this role through the activation of its nicotinic (nAChR) and muscarinic (mAChR) classes of receptors, which are present on distinct categories of neurons within this brain region. The M1 excitatory mAChR is known to mediate ACh action at pyramidal neurons throughout the mPFC and recent expression data suggests that the M3 excitatory mAChR may also activate pyramidal neurons located specifically within layer VI of the mPFC. We tested the contribution of M3 mAChRs toward muscarinic responses in layer VI pyramidal neurons present within acute brain slices from adult mice of both sexes. Active whole-cell responses to muscarine (30 µM) were measured in neurons starting either below or above firing threshold, in the absence or presence of selective M3 mAChR antagonists 4-DAMP (10 nM and 100 nM) and darifenacin (1 µM). Normal muscarine responses in the absence of antagonist elicited an immediate transient inhibition response followed by a prolonged excitation response. Both M3 antagonists abolished the inhibition response when present and decreased the excitation response in a dose-dependent manner that was independent of sex. Ongoing experiments aim to confirm the involvement of M3 mAChRs using a

genetic knockdown approach. Our findings provide functional evidence that M3 mAChRs contribute to ACh modulation of mPFC layer VI pyramidal neurons, and therefore likely play a role in ACh support of normal cognitive functions.

P3-B-35: *A functional model of neocortical microcircuitry for integrating bottom-up and top-down information streams*

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The neocortex is composed of a hierarchy of regions and is thought to perform sensory inference by combining two complementary information streams: 1) a feedforward stream propagating sensory information bottom-up across the hierarchy, and 2) a feedback stream propagating top-down contextual information, representing expectations or priors originating in higher-order associative regions. Within a cortical region, these two streams are integrated at the basal and apical dendrites of layers 2 & 3 pyramidal neurons. How they combine these two streams to update feedforward representations based on contextual priors is unknown. Here, we propose a functional model of integration of these two streams at basal and apical compartments of pyramidal cells based on known physiological principles. We developed a novel visual dataset that implements parameterized ambiguity between classes of handwritten characters, and trained the feedback projection onto apical dendrites using gradient descent to update the sensory representation at the basal dendrites and resolve ambiguity. Our proposed model allows analysis of candidate local learning rules that could support biological learning, and provides a novel insight into how pyramidal neurons and neocortical circuitry could integrate sensory and contextual information to learn predictive models of the world.

P3-B-36: *Microdomain calcium signals in capillary pericytes are independent of changes in membrane potential*

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Mural cells of the brain vasculature exhibit spontaneous calcium (Ca2+) transients in vitro and in vivo. While the voltage-dependent Ca2+ signals that mediate contractility in vascular smooth muscle cells have been well-studied, little is known about the mechanistic properties underlying Ca2+ signaling in capillary pericytes. These cells robustly express the KATP channel Kir6.1 and voltage-gated calcium channels, leading to the belief that their Ca2+ transients are likewise voltage-dependent. Here, we tested the effects of pharmacological and ion substitution experiments, which are known to modulate

pericyte membrane potential, on pericyte microdomain Ca2+ signaling in acute cortical brain slices of PDGFRβ-GCaMP6f mice. Pericyte Ca2+ transients were analyzed with AQuA, an open-source, unbiased software that is free from the inherent assumptions in region-of-interest-based approaches. We report that membrane depolarization by increasing extracellular potassium (K+), or by modulating pericyte K+ channel permeability with KATP channel agonists or antagonists, does not affect the frequency or other properties of pericyte Ca2+ transients. Consistent with these results, blockers of L- and T-type voltage-gated calcium channels did not affect capillary pericyte Ca2+ signaling, in contrast to ensheathing-type pericytes on arteriole-to-capillary transitional segments. These results suggest that, in contrast to vascular smooth muscle cells and ensheathing-type pericytes, capillary pericyte calcium transients are largely independent of their resting membrane potential.

P3-B-37: *A role for dietary restriction and adiponectin administration as therapies in Fragile-X Syndrome.*

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Fragile X Syndrome (FXS) is the most common form of inherited intellectual disability and a leading genetic cause of autism. A promising therapeutic target for FXS involves enhancing AMP-activated protein kinase (AMPK) activity. AMPK can regulate protein synthesis through mTOR inhibition, and in FXS, can rescue deficits in synaptic plasticity/spine morphology. In the current study, we show that intermittent fasting (IF) can regulate rescue deficits in long-term synaptic plasticity in a mouse model of FXS (Fmr1 KO). We then explored whether adiponectin (APN), a protein hormone produced by adipocytes during fasting, could play a role in this process. We found Fmr1 KO mice normally had lower levels of APN, but that exogenous application of APN to hippocampal slices could rescue hippocampal synaptic plasticity in these animals. Short-term incubation with APN also induced a significant increase in GluA1 phosphorylation (Ser 831), and increased surface expression of AMPA receptors. Future studies will examine whether synthetic versions of APN can have beneficial effects in Fmr1 KO animals to determine if this is a potential new therapeutic approach for FXS.

P3-B-38: *Spatial and temporal analysis of interneuron activity during neurovascular coupling*

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Brain activity triggers increases in local energy supply by sending signals to blood vessels that increase blood flow in activated regions of the cortex. This process, known as neurovascular coupling, is used

to map human brain activity in health and disease. However, mounting evidence suggests that inhibitory interneurons can also modulate blood flow by releasing vasoactive compounds such as nitric oxide, raising the question of how different interneuron subtypes interact and control blood flow during sensory processing. Here, we perform optical imaging in mice expressing the calcium indicator GCaMP6f, in either somatostatin or parvalbumin-expressing interneurons. Using a single whisker stimulation model, we measure the spatial tuning of these different inhibitory neuron subtypes across the barrel cortex in relation to changes in blood volume and compare them to excitatory neuronal activity. This work sheds light on the intricate relationship between cell-type specific activity and blood flow control in the healthy brain and is important for interpretation of non-invasive hemodynamic imaging signal, such as BOLD fMRI.

P3-B-39: *Impact of age on functional cholinergic synapses in the prefrontal cortex and an effective treatment to restore nicotinic signalling*

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Cholinergic modulation of the prefrontal cortex is essential for attention and executive function. It has long been suggested that the prefrontal cholinergic system is vulnerable in aging, but the functional impact on cortical synapses is unknown. Here, we systematically interrogate age-related changes in the integrity and pharmacology of prefrontal cholinergic transmission using optogenetic stimulation in brain slices from transgenic mice across a broad adult age range. Our results show specific age-dependent nicotinic deficits: young-adult cholinergic signaling exploits both nicotinic and excitatory-muscarinic receptors, while older-adult responses become predominantly muscarinic. Toward rescue of the nicotinic deficit, we applied the nicotinic positive allosteric modulator (PAM) NS9283. It potentiated younger but failed to restore older responses, suggesting a decline in nicotinic receptor availability. Since PKC signalling can boost nicotinic receptor availability, we asked whether the signaling pathways of intact postsynaptic muscarinic receptors could be harnessed toward nicotinic receptor restoration. While M1 PAM alone proved insufficient, the M1 agonist and cognitive-enhancer xanomeline significantly restored nicotinic responses in brain slices from older mice. Pharmacological investigation confirmed xanomeline potentiation of the nicotinic response is muscarinic- and PKC-dependent. This result highlights a novel approach to treat age-related cognitive decline by harnessing muscarinic signalling to rescue nicotinic deficits at prefrontal cholinergic synapses.

P3-B-40: *Title: Effects of cannabinoid receptor allosteric modulators on spike and wave discharges in the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model of absence epilepsy*

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Childhood absence epilepsy (CAE) is primarily observed in children, with absence seizures consisting of 2.5-5Hz spike-and-wave discharges (SWDs). Current treatments are ineffective in ~1/3 of patients. Targeting the endocannabinoid system (ECS) has potential to reduce SWDs by promoting presynaptic inhibition via type 1 and type 2 cannabinoid receptors (CB1R, CB2R). Previously, we assessed CB1R ligands that are mixed allosteric agonist-positive allosteric modulators (ago-PAMs: GAT211, GAT591, GAT593) and the CB1R PAM (GAT229) for efficacy at reducing SWDs in GAERS, a rat model of CAE. Findings showed all four compounds reduced SWD incidence and/or duration (35-60%). In the present experiment, we assessed GAT588, a CB1R ago-PAM and CB2R agonist, for efficacy at reducing SWDs in GAERS. Given CAE includes enhanced inflammation and cytokine release, we predicted that the anti-inflammatory activity of CB2R activation would translate to a greater reduction in SWDs by GAT588 compared to previous compounds. To that end, local field potentials (LFP) were recorded bilaterally in somatosensory cortex of GAERS and SWDs were assessed following systemic (i.p.) administration of GAT588 (1, 3 and 10 mg/kg). Findings revealed GAT588 modestly reduced SWD incidence (~24%) and duration (~40%) at higher doses, although efficacy tapered off within 2 h. Thus, GAT588 showed equal or less efficacy at reducing SWDs compared to CB1R-specific ligands. One explanation could be that GAT588 binding to CB2R reduces the compound's availability at CB1R. However, future research is necessary to quantify CB2R expression in GAERS and further characterize the role the ECS plays in CAE.

P3-B-41: *Investigating Neural Correlates of Resting-State Hemodynamics across different brain states with wide field optical imaging*

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Resting-state vasodynamics are commonly used across different imaging modalities to infer neuronal activity in health and disease. However, low frequency oscillations in blood flow arise from the integration of both neurovascular coupling and intrinsic vasomotion, and the conditions upon which resting-state hemodynamics accurately report neuronal activity remain controversial. Here we performed simultaneous wide field optical imaging of neuronal calcium signals and intrinsic blood volume changes (HbT) in mice expressing a red calcium indicator (jRGECO1a) in excitatory neurons. We analyze and compare cross-correlations between HbT, HbR, and neuronal calcium in both awake and sedated mice. We further analyze changes in these correlations as mice are habituated to head-fixation. A machine-learning based optimization procedure was used to model a hemodynamic

response function (HRF) based on data from sensory (whisker deflection) evoked responses. Convolution of the neuronal calcium signal with this HRF enabled prediction of HbT signals for both evoked and resting-state experiments. We find that the resting-state correlations between neuronal calcium and blood volume are highly variable, and depend on several factors including brain state. In summary, we report a pipeline for studying resting state activity in the mouse brain, and outline several important parameters to consider. These results shed light on the neural basis of resting state imaging signals, and provide a framework for studying alterations in resting state hemodynamics in pathological conditions.

P3-B-42: *Pannexin-1 transports anandamide to modify synaptic activity*

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Pannexin-1 (Panx1) is an ion and metabolite channel with broad cell/tissue expression, including neurons and glia of the central nervous system. Panx1 is best known for its efflux of ATP, contributing towards a multitude of patho/physiological mechanisms. With the Panx1 cryo-EM structures recently reported, unique gating mechanisms have been uncovered, including a pore-lining N-terminal helix (NTH) rearrangement to allow migration of bilayer lipids into the pore pathway, blocking ion flux. These gating mechanisms could explain how Panx1 channels functionally 'close' to small molecule flux. We recently described a novel role for Panx1 in controlling extracellular concentrations of the endocannabinoid - anandamide (AEA). Here, we hypothesize that Panx1 facilitates AEA permeation across the plasma membrane to regulate uptake of AEA for synaptic clearance and degradation. Using combinations of electrophysiology, fluorescent dye uptake, and mutagenesis in HEK293T cells over-expressing Panx1, we are investigating structural regions within Panx1 that may govern AEA permeability. Our data show Panx1 expression increases the uptake of a fluorescent AEA molecule (CAY10455: CAY). In addition, the application of physiological concentrations of non-labelled AEA alters the uptake of CAY, suggesting the compounds 'compete' for channel permeation. Furthermore, we have found that deletion of the Panx1 NTH introduces a switch of function mutation by knocking out ion flux and increasing CAY permeability. This data proposes a novel route of small molecule permeability through Panx1 channels.

P3-B-43: *Unique cellular and synaptic computations in an excitatory subiculum subtype*

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Understanding how neural circuits give rise to behaviour comes from a thorough knowledge of underlying cell types. The subiculum, a brain region essential for memory, has been classically thought of as containing excitatory pyramidal cells that are relatively homogeneous. Notably, recent transcriptomic work has illustrated that the subiculum contains a diverse set of excitatory neuron subtypes, including a unique group of cells that occupy the deepest layer of the subiculum (hereafter, "deep cells"). Here, we investigated the electrophysiological differences between deep cells and other subiculum pyramidal cells using whole cell patch clamp electrophysiology in acute ex vivo slices. We found differences in intrinsic properties, including marked differences in input resistance, as well as a dendritic organization that lacked radial obliques. In examining synaptic integration, we identified that deep cells have a slow depolarizing response to transient synaptic inputs, enabling deep cell responses to dramatically outlast tuft stimuli. Finally, we also found a profound difference in response to introduction of carbachol (CCH), which binds to both nicotinic and muscarinic acetylcholine receptors. In total, our results illustrate that deep cells likely serve a specialized function in the subicular circuit, likely driven by their enhanced excitability, slow timescales, and selective acetylcholine receptor activation response. Given the important role of neural activity and acetylcholine in memory, deep cells may comprise a critical and unique cell-type substrate of memory in the subiculum.

P3-B-45: *Nitric oxide interferes with endocannabinoid signaling at glutamate synapses in the rat dorsomedial hypothalamus*

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Endocannabinoids (eCBs) are important neuromodulators that act in the dorsomedial hypothalamus (DMH) to regulate food intake, sleep-wake cycles, and the response to stress, presumably by altering neurotransmitter release. eCBs decrease the release of GABA onto DMH neurons, but it remains unknown whether they affect glutamate release, despite observations that DMH neurons receive extensive glutamate input, and type I cannabinoid receptors (CB1Rs) are expressed on glutamate terminals throughout the brain. Here we show using patch clamp electrophysiology that the CB1R agonist, WIN 55,212-2, significantly decreases glutamate release onto DMH neurons in young male Sprague-Dawley rats. We failed, however, to observe eCB-mediated short- or long-term plasticity of glutamate synapses using protocols that trigger eCB release and plasticity of GABA synapses in the DMH. Another neuromodulator, nitric oxide (NO), has been shown to interfere with eCB signaling in other brain regions. We prevented NO synthesis by blocking NMDA receptors or inhibiting nitric oxide synthase, and observed a long-term depression in glutamate signaling under both conditions. Scavenging NO in the synaptic cleft or blocking presynaptic soluble guanylate cyclase did not reveal the same eCB-mediated plasticity, suggesting that NO is interfering with eCB synthesis/ transport in the postsynaptic DMH neuron. Overall, these data suggest that NO hinders the ability of eCBs to modulate glutamate transmission in the dorsomedial hypothalamus in rats. This research could have important implications for eCB and NO interactions across a wide range of physiological functions in the brain.

P3-B-46: *Mapping atypical subiculum excitatory neurons across circuits and behavior*

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Subiculum pyramidal neurons form the main output of the hippocampus, and are classically viewed as giving rise to memory by integrating different forms of proximal and distal dendritic input. Here, we identified a sparse pyramidal cell subpopulation within the subiculum that diverges from classical pyramidal neuron characteristics across connectivity and morphology. Via transcriptomics, we

identified a sparse excitatory neuron population that occupies the deepest layer of the subiculum, and generated a new transgenic mouse line that allows cre-mediated cell-type-specific access of these deep cells. Combining this transgenic line with cell-type-specific viral tracing tools, we discovered that this deep cell population forms dedicated projections to the anterior thalamic nuclei, a key brain region in spatial working memory. Moreover, these deep cells lack radial oblique dendrites typical of classical subiculum pyramidal cells. Motivated by this unique local and long-range structure of these cells, we investigated this population's potential functional correlates via spatial memory paradigms. Altogether, our data provides evidence for a previously unknown subiculum pyramidal cell subtype that exhibits unique structural characteristics and could play a potentially specialized role in spatial memory. Future work will be integral to further clarify the structural characteristics and functional correlates of this atypical population.

P3-B-47: *Homeostatic-like potentiation of the aversive habenulo-raphe pathway in an animal model of post-stroke depression*

Sebastien Maille[1], Sean Geddes[1], David Lemelin[1], Saleha Assadzada[1], Jean-Claude Béïque[1]

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Stroke is one of the leading causes of death and adult long-term disability across the world. Despite increasingly efficient rehabilitation programs, stroke survivors experience an unusually high incidence of depressive symptoms which, beyond the emotional suffering, also undermine recovery outcomes by reducing patient motivation levels. Human and animal studies have linked the incidence of post-stroke depression to the extent of prefrontal cortex (PFC) damage. We hypothesized that PFC stroke promotes the development of depressive phenotypes by triggering maladaptive network remodelling in mood-related networks. The PFC and the epithalamic lateral habenula (LHb) are limbic structures that send powerful, top-down axonal projections to the serotonergic dorsal raphe nucleus (DRN), a key neuronal hub for mood regulation. We used viral, optogenetic and electrophysiological strategies to outline the functional architecture of the PFC and LHb projections to DRN. Then, we found that an endothelin-1-mediated stroke in PFC triggers a time-dependent remodeling of the glutamatergic input from the LHb to DRN 5-HT neurons. This remodeling resulted in 1) an increased AMPAR/NMDAR ratio, 2) insertion of GluA2-lacking AMPARs, 3) increased quantal size, and 4) faster decay kinetics of quantal excitatory postsynaptic currents. Because the LHb-DRN pathway is believed to encode emotionally salient features such as aversion and anticipation of threat, a homeostatic-like upregulation of this pathway may contribute to the depressive symptomology following stroke.

P3-B-48: *Investigating the role of ATF4 in astrocyte reactivity and neurodegeneration*

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During central nervous system injury and neurodegenerative disease, it is well established that astrocytes may become reactive. This change has been implicated in neurotoxicity, however, the mechanisms that promote astrocyte reactivity remain to be fully understood. The Integrated Stress Response (ISR) is a cell signaling pathway that is activated in response to cellular stress and has been shown to be activated in injured astrocytes. Although, we have previously shown that the central regulator of the ISR, activating transcription factor-4 (ATF4), promotes neuronal death, its role in astrocytes and non-cell autonomous neurodegeneration remain relatively unexplored. Given this, our current study focused on evaluating the role of ATF4 in astrocyte reactivity. Using primary mouse astrocytes, we show conditioned media from activated microglia, as well as direct addition of A1 inflammatory cytokines results in ATF4 upregulation. Furthermore, ectopic overexpression of ATF4 in astrocytes is sufficient to induce a reactive phenotype, and conditioned media from these cells was sufficient to promote neuronal loss of primary neurons. To determine whether ATF4 is required for this process, reactivity markers were assessed in wildtype and ATF4-null astrocytes. It was found that stress-induced reactivity was attenuated in ATF4-deficient astrocytes. Importantly, conditioned media from astrocytes lacking ATF4 was less neurotoxic than wildtype astrocytes. These results reveal a novel role of ATF4 in regulating astrocyte reactivity and the resulting neurodegeneration.

P3-B-49: *An in vitro model of synaptic reconsolidation in acute rodent hippocampal slices*

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Memory reconsolidation is a fundamental process by which old memories can be destabilized and subsequently modified upon retrieval. Memory reconsolidation has classically been studied with behavioural assays; however, it is difficult to dissociate systems-level versus cellular-level effects using these methods. To directly study the cellular mechanisms of reconsolidation, we are developing a novel in vitro model of memory reconsolidation in the rodent hippocampus using brain slice electrophysiology. Lasting increases in synaptic strength, referred to as long-term potentiation (LTP) and believed to underlie memory formation in the hippocampus, can be measured using field electrophysiological recordings. There is evidence that synapses that have been strengthened during learning are weakened during memory reconsolidation. However, no group has yet been able to study the complete process of synaptic reconsolidation in an in vitro brain slice model. To determine whether reconsolidation can be initiated in acute hippocampal slices obtained from 7-12-week-old male C57BL/6 mice, LTP will be induced at CA3-CA1 synapses, and potentiated synapses will be subsequently reactivated in analogy to memory recall in vivo. To date, we have obtained preliminary

evidence for activity-dependent plastic modification of CA3-CA1 hippocampal synapses resembling reconsolidation. This novel in vitro model of reconsolidation provides a unique opportunity to directly assess the underlying molecular mechanisms of reconsolidation in contrast to in vivo methods commonly employed in the field.

P3-B-50: *Stress induces calcium activity in oxytocin neurons and astrocytes in the mouse PVN in vivo*

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Neurons and astrocytes in the hypothalamic paraventricular nucleus (PVN) exist in a structurally compact microenvironment where bidirectional communication between the two cell types influence the physiological and behavioral output of this brain region. It is well known that oxytocin (OT) neurons in the PVN are strongly stimulated by social interactions. Stressful stimuli can also stimulate OT secretions to buffer central and peripheral stress responses. However, the mechanism by which stress stimulates OT neuronal activity is unclear. Norepinephrine, a stress hormone, has been shown to stimulate PVN neuronal activity via astrocyte-dependent mechanisms in vitro (Gordon et al., 2005; Chen et al., 2019). Therefore, we hypothesized a potential involvement of astrocytes in stress-induced activation of OT neurons. To begin testing this hypothesis, we first examined the activity of PVN astrocytes and OT neurons using fiber photometry in freely behaving mice (n=4-6 mice) under different behavioural contexts. Social interactions (sniffing) increased Ca2+ signals in PVN OT neurons ($p=0.03$) as expected, but decreased Ca2+ signals in PVN astrocytes ($p=0.003$). Interestingly, stressful stimuli (looming shadow) increased Ca2+ signals in both OT neurons ($p=0.04$) and astrocytes ($p=0.04$). These results indicate that stress stimulates both astrocyte and OT neuronal activity in vivo. To better understand how the two cell populations interact and influence each other's activity, we are currently performing simultaneous recording of PVN astrocytes and OT neurons both in vivo and in vitro.

P3-B-51: *Multiplexing distinct inputs by regulation of spike synchrony in the dorsal raphe nucleus*

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[1]University of Ottawa

The serotonergic dorsal raphe nucleus (DRN) receives diverse long-range synaptic inputs, yet the relative contribution of each input to DRN output spiking patterns is unknown. Here, we use electrophysiological, optogenetic and computational tools to compare functional features of excitatory inputs from lateral habenula (LHb) and prefrontal cortex (PFC) onto DRN 5-HT neurons. Dual-color opsin strategies revealed that single 5-HT neurons receive functionally matched input from

both PFC and LHb. Subthreshold features of excitatory post-synaptic potentials, including amplitude and decay, were largely overlapping. However, PFC inputs triggered spikes that displayed significantly higher latency and greater jitter than those from LHb. A support vector machine classifier demonstrated that input identity can be accurately decoded from the spike timing of under ten 5-HT neurons, revealing that these timing differences can be robustly parsed by downstream circuits. By examining the intrinsic cellular mechanisms in 5-HT neurons underlying these transformations of EPSPs to spikes, we uncovered a prominent T-type calcium conductance which selectively boosts certain input types, as well as subthreshold, voltage-dependent membrane noise which calibrates spike jitter and latency. Together, these results outline a mechanism by which intrinsic properties of 5-HT neurons functionally segregate LHb and PFC inputs into distinct spiking patterns which could, we hypothesize, be decoded by downstream areas innervated by 5-HT axons - a multiplexing operation.

P3-B-52: *Characterization of prefrontal cortex excitatory and inhibitory activity through optogenetics and pharmacology on large-scale multi-electrode arrays*

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The ability of brain regions to regulate information processing depends intimately on how distinct cell types are functionally organized into networks. In the prefrontal cortex (PFC), an elaborate repertoire of activity arises from the interaction of single excitatory (E) and inhibitory (I) neurons. It remains unclear, however, how each neuronal subtype contributes to the overall spiking activity of the surrounding network. To examine the contribution of different neuronal subtypes to cortical dynamics, we recorded and stimulated spiking activity in acute slices of PFC using high-density multi-electrode arrays containing 4096 closely spaced electrodes. To parse out the contribution of distinct cell types, we first developed a spike sorting technique utilizing waveform kinetics and spline interpolation to distinguish putative regular-spiking excitatory neurons from fast-spiking inhibitory interneurons. We validated this classification using a combination of optogenetic and pharmacological strategies. Using a sequential pharmacological approach, we systematically tested the contribution of each connection type to the activity patterns of each cell type. In intact networks, activating parvalbumin (PV) neurons had no effect on their firing rate, indicating complex compensatory mechanisms in the network. However, with GABAergic and glutamatergic transmission blocked, activating PV neurons reliably increased their firing rate. Together, these results provide insights on how complex connectivity motifs can affect respective E and I cell population activity.

P3-B-53: *Stem Cell-Derived Multi-Lineage Assemblies to Investigate the Determinants of Human Microglial Integration, Identity and Function*

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Microglia are a unique subset of macrophages that reside in our brain. Under normal condition, they sculpt synaptic structures, provide neuronal trophic support and engulf apoptotic cells. As the main immune cells of the brain, microglia constantly survey their surrounding areas and can orchestrate potent responses to brain damage and immune stimuli. Dysregulation of microglial function has been associated with multiple devastating neuronal diseases. Unlike neurons or glial cells, microglia have a unique developmental origin. They emerge from the yolk sac during primitive hematopoiesis, subsequently invade the brain and establish residence during early stages of embryogenesis. Brain residence is essential for microglia to adopt their mature functional form and reciprocally crucial for normal brain development. Little is known about the mechanisms underlying these coordinated developmental processes. To faithfully track the profile of human in vivo microglia, recapitulate their developmental trajectory ex vivo, and study the coordinated development of brain and microglia, we established 3D co-cultures between human pluripotent stem cell-derived microglia and neuro-glial cells. We also invented a new platform where we engineer the fusion of cerebral and yolk sac organoids, using this modular design to assemble them and study microglia-brain integration. Based on these platforms, we are further examining responses of microglia to different engineered brain environment. The knowledge gained from this study will continue to support our disease-modeling efforts and improve our capability of generating bona fide microglia for therapeutic applications.

P3-B-54: *Implications of reduced inhibition in schizophrenia on human prefrontal microcircuit activity*

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Reduced performance when processing auditory oddball stimuli is commonly seen in schizophrenia and is associated with a reduced mismatch negativity in EEG signals from the prefrontal cortex. Post-mortem gene-expression studies indicate that a reduced inhibition by parvalbumin-expressing (PV) interneurons plays an important role in the functional and brain signal deficits in schizophrenia, but this link remains to be established. We integrated human cellular, circuit and gene-expression data into detailed computational models of human cortical PFC microcircuit in health and schizophrenia, to mechanistically link the altered PV interneuron inhibition to deficits in oddball processing and EEG signals. We found an increased baseline activity in schizophrenia microcircuit models due to reduced PV interneuron inhibition, and we differentiated the role of the two implicated mechanisms - reduced PV interneuron inhibition onto other neurons vs reduced NMDA conductance onto PV interneurons. We then modelled the response activity during oddball processing to study the implications of

reduced PV interneuron inhibition on cortical processing, and to identify EEG biomarkers of the circuit changes in schizophrenia. Our study integrates diverse human data to mechanistically link circuit changes to cortical function deficits and biomarkers in brain signals.

P3-B-55: *Arc as a critical regulator of spinal cord synaptic plasticity and reconsolidation.*

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The spinal cord is a critical hub for sensory processing, where external stimuli can modulate the synaptic strength of sensory pathways. This dynamic modulation, known as synaptic plasticity, can be regulated by the trafficking and subunit composition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) on the post-synaptic membrane. Nociceptive pathways in the spinal dorsal horn (SDH) can undergo synaptic reconsolidation, where reactivation of synaptic pathways will lead to a brief window of malleability before consolidation. During this window, disrupting spinal reconsolidation by inhibiting protein synthesis can lead to weakening of previously potentiated pathways by synaptic depotentiation. However, the mechanism underlying synaptic depotentiation during disrupted reconsolidation has not yet been elucidated. Here, we modelled spinal reconsolidation using peripheral Capsaicin injections to induce mechanical hyperalgesia as well as activate and reactivate nociceptive pathways in the SDH. We discovered that Arc is acutely expressed in the SDH after Capsaicin injection, with high synaptic membrane expression. During disrupted reconsolidation, mutant (MUT) mice with impaired Arc mRNA dendritic trafficking did not experience reversal of hyperalgesia compared to wild-type mice. MUT mice exhibited altered protein expression of AMPAR scaffolding proteins in the SDH. Inhibiting Arc interaction with endocytic machinery during disrupted reconsolidation was also sufficient to prevent reversal of hyperalgesia. These findings suggest that Arc may play a key role in modulating spinal synaptic plasticity via AMPAR trafficking.

P3-B-56: *Brief synaptic inhibition persistently interrupts firing of fast-spiking interneurons*

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Input-output operations performed by neurons rely on their ability to integrate synaptic activity with their intrinsic electrical properties, a process thought to be constrained by the duration of synaptic events. At variance with this classical view, we find that the sustained firing of CA1 hippocampal fast-

spiking (FS) parvalbumin-expressing interneurons (PV-INs) is persistently interrupted for several hundred milliseconds following brief GABAAR-mediated inhibition. A single presynaptic neuron could interrupt PV-INs, occasionally with a single action potential (AP), and reliably with brief bursts of APs. Experiments and a computational model revealed that the persistent interruption of firing maintains neurons in a depolarized, quiescent state through a cell-autonomous mechanism dependent on an inactivating Kv1.1-mediated current and largely inactivated Na+ channels. Strikingly, interrupted PV-INs are highly responsive to Schaffer collateral inputs, with subthreshold stimuli at rest becoming suprathreshold during the interruption. We show that the persistent interruption of firing represents a powerful disinhibitory mechanism that favors spike generation in CA1 pyramidal cells. Overall, our results demonstrate that neuronal silencing can far outlast brief synaptic inhibition owing to a well-tuned interplay between neurotransmitter release and postsynaptic membrane dynamics, thus impacting circuit function.

P3-B-57: *Adaptive purinergic P2X7 and P2Y2 signaling following spinal cord injury in Danio rerio*

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In contrast to mammals, zebrafish (Danio rerio) undergo successful neural regeneration following spinal cord injury (SCI). Radial glia lining the zebrafish central canal function as resident neural progenitors. In response to SCI, these cells undergo a massive proliferative response before differentiating into both neurons and glial cells; however, the molecular mechanisms that underlie these processes remain elusive. Among the signaling pathways that are dysregulated following mammalian spinal cord injury is the purinergic system. In addition to its well-known role as energy currency in cells, ATP and its metabolites are small molecule neurotransmitters that mediate diverse cellular processes. Previous reports have identified roles for purinergic P2X7 and P2Y2 receptors in mammalian neural progenitor cell proliferation and neuronal differentiation. Given that the purinergic system is evolutionarily conserved among vertebrates, we hypothesize that radial glia proliferation and neurogenesis following zebrafish SCI may be mediated by P2X7 and P2Y2 signaling. Immunohistochemical data shows co-localization of radial glia cell marker GFAP+ with P2X7 and P2Y2 receptors. Western blotting data shows significant upregulation of P2Y2 receptor expression at 1 day post SCI, as well as significant downregulation of P2X7 receptor expression at 7 days. Preliminary immunohistochemical data suggests that P2Y2 receptor antagonism increases proliferation around the central canal beyond spontaneous levels at 7 days post injury. As our understanding of this signaling system and pro-regenerative conditions continues to evolve, so does the potential for the development of novel therapeutic interventions for SCI.

3C. Disorders of the Nervous System

P3-C-58: *The therapeutic benefits of Activin A in Huntington disease*

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Huntington disease (HD) is a monogenic disorder with autosomal dominant inheritance. In HD patients, neurons involved in motor function degenerate leading to motor and cognitive impairments. Dysregulation of synaptic function and calcium handling is common in many neurodegenerative diseases including HD. Our lab has shown that nuclear calcium signaling in cultured striatal neurons is altered in HD mice (unpublished data). Furthermore, recent work from the Bading lab has shown that overexpression of Activin A, a protein whose transcription is nuclear-calcium-dependent, reduces toxic extrasynaptic NMDA receptor signaling in the hippocampus. Taken together, the goal of this project is to determine whether Activin A is reduced in HD, and whether upregulating it can reduce synaptic dysfunction and ameliorate the performance of HD mice on a motor task. Cortical-striatal co-cultures and the YAC128 HD mouse model were used. Our data shows that Activin A is indeed decreased in HD culture media, and its overexpression normalizes extrasynaptic NMDA receptor expression. Moreover, early injection of an Activin A AAV virus into the striatum led to a significant improvement in a motor coordination task at an age where HD mice are known to show impairment. This project has brought to light the potential therapeutic benefits of Activin A in the treatment of HD; more research needs to be done in order to understand Activin A's mechanism of action, as well as further explore its potential benefits in other neurodegenerative diseases.

P3-C-59: *Senescent-like neurons accumulate after traumatic brain injury possibly limit the therapeutic potential of senolytic drug ABT263*

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Mild traumatic brain injury can lead to long-term neurological impairment and a propensity towards neurodegenerative disease later in life, although the molecular mechanisms driving this are unclear. The objective of this study is to characterize and target cellular senescence in a mouse model of mTBI. Methods: In the current study, sex-balanced groups of C57BL/6 mice received three mTBIs, each 24h apart, or sham procedures, followed by behavioural testing or tissue analysis one week later. Results: We found that closed skull mild injury elicited prolonged righting reflex, neurocognitive impairment

in the Morris water maze test, and evidence of gliosis and microgliosis despite the absence of any gross lesion in both males and females. In the cortical and hippocampal region near injury site, we found evidence of DNA damage (double strand breaks, oxidative damage, and R-loops), senescence (elevated p16 and p21), and neuroinflammation in a sex-specific manner. Single-cell RNA sequencing revealed neurons with senescent-like features, including the DNA damage response and the senescence-associated secretory phenotype (SASP), and cell-type specific changes consistent with innate immune activation, synaptic dysfunction indicating excitotoxicity, gliosis, and metabolic reprogramming. Treatment with the senolytic agent ABT-263, which selectively eliminates senescent cells, improved behavioural performance and reduced markers of DNA damage and senescence, but did not significantly reduce inflammation. Conclusion: This study shows compelling evidence that senescence is a viable clinical target, but we conclude that more targeted strategies towards inflammation that do not eliminate cell populations and that may be sex-specific will be critical in the future treatment of mTBI.

P3-C-60: *Transcriptomic and epigenomic alterations in neurons in a mouse model of multiple sclerosis*

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Multiple sclerosis is a neuro-immune disease that leads to demyelination of axon tracts in the central nervous system, and neuronal cell damage and death. The disease frequently affects the eye and optic nerve with visual loss as a presenting symptom in as many as 50% of patients. Demyelinated axons are then exposed to an adverse environment and loss of trophic support by the myelin sheath. We were interested in understanding how this inflammation of the central nervous system may induce transcriptional and epigenetic changes in the gene signature within the neurons. We used a mouse model of multiple sclerosis and, at four different timepoints of the disease, isolated retinal neurons using fluorescence activated cell sorting. We are able to obtain up to 50,000 cells per mouse and using immunocytochemistry have demonstrated that these are retinal ganglion cells. From these cells, we collected RNA for RNA-sequencing, and DNA for chromatin accessibility sequencing from the four different timepoints. With this data, we expect to be able to visualize changes in gene expression and concurrent changes in the gene regulatory regions in the neuronal genome occurring in response to pathological inflammation.

P3-C-61: *Enhancing recovery with the administration of a subcommissural organ-spondin derived peptide in a rat clip compression-contusion model of traumatic cervical spinal cord injury (SCI)*

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NX210c is a 12-amino acid peptide derived from the subcommissural organ-spondin, with a multifunctional mechanism of action to ameliorate outcomes following neurological disorders and injuries. This study aims to evaluate the efficacy of NX210c to promote repair and functional recovery in a traumatic cervical SCI model. Adult female rats were subjected to a C6/C7 clip compression-contusion injury and treated once daily for 8 weeks with intraperitoneal injections of NX210c (8 mg/kg) or its vehicle beginning 4h or 8h post-injury (n=15-17/group). Early administration of NX210c increased forelimb strength (grip strength) and improved several static and dynamic aspects of locomotion including interlimb coordination, (i.e., regularity index or base of support of the forelimbs; CatWalk). When delaying first administration to 8h post-injury, NX210c promoted weight gain, accelerated bladder control recovery from 14 to 9 days post-injury, and reduced sensorimotor deficits (inclined plane). Regardless of the therapeutic window, more SCI rats with weight support were observed following NX210c treatment. Preliminary histology (n=3/group) demonstrates higher white matter preservation and reduced cavity size at the injury site with NX210c treatment beginning at 8h post-injury compared to vehicle. To summarize, NX210c improves motor function and bladder control, while also contributing to improved white matter preservation. We anticipate that this study will provide a strong proof of concept for the use of NX210c as a treatment for acute SCI patients.

P3-C-62: *Peripheral metabolic impacts of ketogenic interventions in the 3xTg model of Alzheimer's disease*

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Metabolic risk factors contributing to Alzheimer's disease (AD)-associated dementia can be prevented by protective lifestyle remodelling. Since ketogenic diet interventions promote clinical improvements during early-stage cognitive disabilities, we investigated their effects on the liver, a key metabolic regulator. 3xTg-AD and B6;129 (wild type) mice were administered a control diet (CD, 70% carbohydrate, 20% fat, 10% protein), a CD supplemented with a ketone-yielding substrate (medium chain triglycerides, MCT diet), or an extreme carbohydrate-free ketogenic diet (KD). RNA sequencing of the liver after 6 months of diet showed that Wild type and 3xTg-AD mice on CD exhibited more than 800 differentially expressed genes (DEGs) involved in mitochondrial functions, metabolic pathways of

lipids, ketones, carbohydrates, and xenobiotic metabolism. Interestingly, the MCT diet and KD diets normalized different classes of these DEGs and triggered distinct diet-specific genetic pathways. In line with this, the physiological effects of these two ketogenic interventions markedly differed with regard to their effects on glucose handling and whole-body energy metabolism. These data highlight the development of peripheral metabolism disturbances in AD mice and underscore that clarifying the physiological mechanisms underlying the beneficial effects of ketogenic interventions is needed in order to fully harness their therapeutic potential.

P3-C-63: *Investigating the effects of IDO1 inhibition on neurological recovery following experimental TBI*

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Background: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. The enzyme indoleamine 2,3 dioxygenase 1 (IDO1) catalyzes the rate-limiting step in the kynurenine pathway (KP), which produces both neuroprotective and neurotoxic metabolites. Increased IDO1 activity has been described in several neurological disorders, including TBI, but its effect on TBI outcomes remains unclear. Objective: Determine if IDO1 inhibition improves neurological recovery after experimental TBI. Methods: Young adult male Sprague-Dawley rats underwent fluid percussion injury (FPI) or sham injury, followed by oral dosing of an IDO1 inhibitor (PF-06840003, 100 mg/kg) or vehicle ((2-Hydroxypropyl)- β-cyclodextrin (HBCD)) twice daily. Over the following month rats were tested on the Barnes Maze, rotarod, neuroscore, and open field test at various timepoints. Statistical analyses were performed to determine effects of FPI and IDO1 inhibition on neurological recovery. Results: FPI led to worse performance on the neuroscore, rotarod, and Barnes maze compared to sham injury. Injured rats receiving IDO1 inhibitor had improved performance on neuroscore and rotarod testing as compared to injured vehicle controls. IDO1 inhibition also improved performance on the long-term memory probe trial in the Barnes maze. Conclusion: Inhibition of IDO1 activity improves neurological function after experimental TBI. Further work is needed to determine the effect of IDO1 inhibition on specific KP metabolites and various secondary injury mechanisms after TBI.

P3-C-64: *Evidence for early, vasculature-associated changes in the hypothalamus of the 3xTg model of Alzheimer's disease*

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Alzheimer's disease (AD) is the leading cause of dementia worldwide, and no effective treatments are yet available for this devastating disease. Development of new therapeutic approaches will be improved through deeper understanding of the early steps during disease pathogenesis. The hypothalamus is a major regulator of energy metabolism, controlling whole-body activity, adiposity, glucose homeostasis and lifespan, and its involvement in AD remains relatively understudied. Given its importance in the bidirectional communication between the brain and periphery, we asked whether the hypothalamic Blood-Brain-Barrier (BBB) shows evidence of changes at early stages in the 3xTg-AD model of AD. We first established an optimized single cell RNA sequencing (scRNAseq) protocol for studying cell populations of the hypothalamus using the BD Rhapsody platform. We then focused our analyses specifically on hypothalamic BBB cells, notably endothelial cells and pericytes. Interestingly, at early, presymptomatic time points, the 3xTg hypothalamus already exhibited transcriptomic disturbances in lipid metabolism, inflammatory and other biological processes in these cells. These findings corroborate the hypothesis that early changes in hypothalamic signaling pathways, hypothalamic inflammation, or hypothalamic vasculature are involved in the global physiological alterations observed in AD models. We are currently mining these data to identify novel potential targets for intervention in AD-associated metabolic disturbances.

P3-C-65: *Consequences of deficient DNA repair on sex-specific outcomes following mild traumatic brain injury*

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Mild traumatic brain injury (mTBI) impacts millions of individuals every year, resulting in symptoms that negatively affect mood, alertness, and cognition. Moreover, different outcomes are often reported in women compared to men. Previous research investigating humans with history of mTBI identified an upregulation in DNA damage with a corresponding downregulation in DNA repair. In particular, breast cancer type I (BRCA1), associated with genomic stability and neuron maintenance in the brain, was significantly downregulated with injury. Therefore, this research examines BRCA1 in deficient DNA repair and its contribution to sex-specific outcomes post-mTBI. Using mice heterozygous for BRCA1 (HET) with a closed-skull cortical impact model of mTBI, outcomes were evaluated at 1- and 6-weeks post injury. BRCA1 deficiency was associated with elevated levels of DNA damage 1-week post-mTBI, with worse cognition and reduced anxiety-related behaviours observed in males compared to females. At 6-weeks post-injury, a downregulation in DNA repair was observed, with persistent neuroinflammation and behavioural impairments in WT injured and HET mice, although BRCA1 deficiency did not exacerbate outcomes as seen at 1-week. Interestingly, a compensatory mechanism was evident in females with BRCA1 deficiency compared to wildtype mice, however further investigation is required. Overall, these results show the adverse effects of DNA

repair deficiency to brain function post-mTBI, and its contribution to behavioural outcomes in a sex-specific manner.

P3-C-66: *Glial activity in the cerebellum may contribute to the ataxic phenotype in an ARSACS mouse model*

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Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early-onset neurodegenerative disease caused by loss-of-function of the SACS gene that encodes the protein Sacsin. It is characterized by progressive loss of motor coordination and cerebellar degeneration. In the cerebellum of SACS knockout mice, we have shown progressive Purkinje cell disfunction and degeneration, as well as altered synaptic innervation into cells of the cerebellar nuclei (CN). A key player in neuronal and synaptic homeostasis are glial cells. Dysfunction of glial cells has been shown to contribute to the pathophysiology of several neurodegenerative disorders including many spinocerebellar ataxias. Here we explore whether glial function is dysregulated in a mouse model of ARSACS. We quantified the reactive astrocytes and microglia in the cerebellum (both in the cerebellar cortex and in the CN) of SACS knockout mice at different stages of disease progression. We found increased astrocyte reactivity as seen by increased GFAP labeling in the CN of ARSACS mice. The astrocyte activation occurs prior to any cell death in the CN or of Purkinje cells. These findings suggest that early dysregulation of astroglia may contribute to the pathogenesis of ARSACS.

P3-C-67: *Dendritic stimulus processing deficits in human cortical microcircuits in depression*

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Reduced inhibition from somatostatin (SST) interneurons and dendritic atrophy of pyramidal (Pyr) neurons are implicated in underlying cognitive deficits in treatment-resistant major depression disorder (depression). Cortical SST interneurons primarily inhibit the apical dendrites of Pyr neurons to facilitate feedforward inhibition and modulate input integration. To study the effects of reduced inhibition from SST interneurons and dendritic atrophy on dendritic stimulus processing, we expanded our previous data-driven models of human cortical microcircuits in health and depression to include active dendritic properties in Pyr neurons such as backpropagating action potentials, and dendritic atrophy in terms of synapses loss and reduced length. We then characterized the functional implications of reduced SST interneuron inhibition and dendritic atrophy in depression on dendritic

processing of stimuli by comparing the signal-to-noise ratio and stimulus detection errors in microcircuit response to top-down (apical dendritic) and bottom-up (perisomatic) inputs. Our study thus mechanistically links circuit inhibition changes in depression to deficits involving processing of stimuli in cortical neuronal dendrites.

P3-C-68: *Altered electrophysiological properties and excitatory network function of corticomotor neurons in C9orf72 loss-of-function mice*

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ALS is the most common motor neuron disease in humans, whereby upper and lower motor neurons degenerate, eventually resulting in death. A major hypothesis underlying the mechanistic origin of neurodegeneration in ALS postulates that cortical hyperexcitability facilitates cell death. Previous research has identified the G4C2 hexanucleotide repeat expansion in the C9orf72 gene as the most common genetic cause of ALS; however, little is known about the contribution of the C9orf72 gene to neuronal excitability in the primary motor cortex. Thus, using a C9orf72 knockout loss-of-function (C9-KO LOF) mouse model, we assessed the intrinsic firing excitability of corticomotor neurons using whole-cell patch-clamp recordings made from acute brain slices. We have found that after disease onset, the action potential firing frequency is significantly higher in the C9-KO LOF mice compared to wildtype mice, highlighting cortical excitability at this timepoint. Moreover, we have found a significant reduction in spontaneous and miniature excitatory postsynaptic current frequency, as well as a significant increase in miniature excitatory postsynaptic current amplitude in the C9-KO LOF mice compared to wildtype mice, suggesting impaired basal excitatory network function. Further investigation into the local inhibitory circuitry will reveal essential information about the neurophysiological mechanisms underlying neurodegeneration in C9orf72 ALS patients, which could contribute to the development of future therapeutic strategies.

P3-C-69: *Pleiotrophin as a modulator of neurite outgrowth, neuroinflammation and OPC differentiation in the presence of CSPGs*

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After CNS injury such as ischemic stroke, chondroitin sulphate proteoglycans (CSPGs) are produced by glial cells in extracellular matrix surrounding the injury. CSPGs are growth inhibitory, reducing axonal sprouting growth and migration of OPCs and thereby impairing recovery. Pleiotrophin (PTN),

a growth factor and a cytokine, is upregulated in the central nervous system (CNS) during development and after injury. It has been proposed that PTN binds to CSPGs in the extracellular matrix to reduce CSPG inhibition of neuron and OPCs growth. However, the effect of CSPGs and PTN on different classes of glial cells is not well described. Here, we investigated the effect of PTN and PTN signaling on primary neuronal and glial cultures. First, neurons were plated on growth inhibitory CSPG matrices or growth permissive laminin matrices and treated with varying concentrations of PTN. Notably, PTN induced growth was dependent on activation of ALK receptor suggesting that PTN can induce growth even in inhibitory environments such as in the CNS after injury. Next, OPCs, microglia and astrocytes were isolated from mixed mouse glia cultures and plated on growth inhibitory CSPG matrices or growth permissive laminin matrices and treated with varying concentrations of PTN. PTN increased the proliferation of OPCs and their differentiation to mature oligodendrocytes in CSPGs matrices. Microglia plated on CSPGs matrix induces the breakdown of CSPGs inducing the release of BDNF and IL 10 with increased phagocytosis and proliferation of microglia. Combined, these data suggest that PTN signaling modulates axonal growth, remyelination process and promotes anti-inflammatory response even in inhibitory environments, thus may have potential as a pro-plasticity therapy following CNS injury.

P3-C-70: *The anatomy of cortical slowing predicts cognitive and motor impairments in Parkinson's disease*

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Frequency-defined patterns of cortical neural activity serve diverse cognitive and sensorimotor functions in health and disease. In patients with Parkinson's disease (PD), a well-replicated literature has reported spatially nonspecific activity increases in slow cortical rhythms alongside decreases in faster activity relative to healthy older adults. These observations have led to a hypothesis of pathological neural slowing in this patient group. However, the lack of a continuous model of such slowing has made this hypothesis difficult to verify, and has stymied efforts to understand its significance to the hallmark motor and cognitive impairments of PD. In this study, we use magnetoencephalographic (MEG) millisecond imaging to derive brain maps of neural slowing from 79 patients with PD relative to a matched group of 65 healthy adults. We provide evidence of a spatially-overlapping slowing of cross-spectral neural activity in PD, which predicts clinical motor impairment measured by the Unified Parkinson's Disease Rating Scale part III and domain-specific cognitive functions quantified using an extensive battery of neuropsychological tests. These results primarily indicate pathology and are spatially-diverse; slowing of neural activity in the prefrontal, somatomotor, and superior temporal cortices each predict different clinical features. Taken together, these

observations are the first evidence for anatomically-specific cortical slowing in PD, and provide potential new targets for non-invasive patient monitoring and future neurostimulation therapies.

P3-C-71: *The netrin-1 receptor DCC promotes the survival of a subpopulation of midbrain dopaminergic neurons: relevance for ageing and Parkinson's disease*

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Mechanisms that determine the survival of midbrain dopaminergic neurons (mDAs) in the adult CNS are not fully understood. In the mature CNS, mDA neurons express particularly high levels of netrin-1 and its receptor DCC. Recent findings indicate that overexpressing netrin-1 protects mDA neurons in animal models of Parkinson's disease (PD), with a proposed pro-apoptotic dependence function for DCC that triggers cell death in the absence of ligand. Here we sought to determine if DCC influences mDA survival. We deleted DCC from mDA neurons using DATcre/loxP gene-targeting and examined neuronal survival in young adult and aged mice. Reduced numbers of mDA neurons were detected in the substantia nigra pars compacta (SNc) of young adult DATcre/DCC fl/fl mice, with further reduction in aged mice. Aged mice also exhibited a gene dosage effect, with fewer SNc mDA neurons in DATcre/DCC fl/wt heterozygotes. Loss of mDA neurons in the SN was not uniform but limited to ventral tier mDA neurons, while mDA neurons in the dorsal tier, which resist degeneration in PD, were spared in both young and aged mice. In the ventral tegmental area (VTA), young mice with conditional DCC deletion had normal mDA neuronal numbers, while significant loss occurred in aged DATcre/DCC fl/fl and DATcre/DCC fl/wt mice. Our results indicate that DCC is required for the survival of subpopulations of mDA neurons and may be relevant to the degenerative process in PD. Our ongoing studies are investigating the distribution and function of subregion-specific expression of netrin-1 by mDA neurons.

P3-C-72: *Chronic social defeat stress alters synaptic transmission at the lateral hypothalamic - dorsal raphe nucleus pathway*

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Disturbance of the central serotonin system has long been thought of playing a leading role in major depressive disorder. The main serotonergic nucleus of the brain, the dorsal raphe nucleus (DRN), integrates inputs from multiple brain regions, a large fraction of which is coming from the lateral hypothalamic area (LHA). In this study, we have examined whether plasticity at the LHA-DRN pathway

contributes to the development of depressive or resilient phenotypes in mice undergoing chronic social stress. To activate LHA terminals in DRN, an AAV-ChR2-YFP was injected in the LHA of 6 weeks old C57BL/6J male mice. Two weeks later, these mice were subjected to chronic social defeat stress (CSDS) protocol. 24-h after CSDS, mice were classified as either susceptible or resilient when evaluated in a social interaction test, and acute brain slices encompassing the DRN were prepared. During whole-cell patch-clamp recordings of DRN neurons, 5 ms blue light pulses were delivered to activate LHA axons terminals, and postsynaptic currents were measured to investigate pre- and postsynaptic plasticity. In resilient mice, we found a significant increase in paired-pulse ratio at GABAergic synapses, indicating the decreased GABA release probability. In susceptible mice, we measured an important trend toward a decrease in the AMPAr/NMDAr ratio, indicating synaptic depression at the LHA-DRN pathway caused by CSDS. These results suggest that synaptic dysfunction at the LHA-DRN pathway may play an important role in the behavioral phenotype found in depression.

P3-C-73: *A splice variant of presenilin-1 associates with indicators of aging and markers of late-onset Alzheimer disease; is this a 'missing link' in aging-related neuropathology?*

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Heterogeneity in the aging process could underpin some of the variability in age of onset of Alzheimer disease (AD). While screening AD brain samples for risk genes, we observed a splice variant of the gene that encodes for presenilin-1 (PS-1), the protein that cleaves the Amyloid Protein Precursor (APP) to yield the β-amyloid (Aβ) fragment. We chose to investigate whether the expression of this variant, e.g. PS-1Δ, could alter the function of wildtype PS-1, e.g. PS-1(WT). Transient overexpression of PS-1Δ in N2a (murine neuroblastoma) cells alters APP processing and also leads to folding of the nuclear membrane (nuclear blebbing; a hallmark of aging). Stable expression of PS-1Δ in C. elegans (worm) affects egg-laying in a wildtype background. Using a loss-of-function sel-12 (homologous to PS-1), we demonstrated that PS-1(WT) rescues the sel-12-dependent egg-laying defect, whereas PS-1Δ does not. Notably, PS-1Δ causes nuclear blebbing in C. elegans. Using proprietary antibodies, we found that the expression of PS-1Δ correlates with the expression of PS(WT) in autopsy brain samples from males, but not females. As importantly, the expression of PS-1Δ correlates with levels of Aβ(1-42), particularly in females who also carried the APOE ε4 risk gene for AD. We are currently exploring whether PS-1Δ represents a factor in the heterogeneity of aging and whether it could be developed as a novel molecular marker of aging as well as a marker of risk for age-related diseases, including AD.

P3-C-74: *Reverse engineering Parkinson's disease risk in a dish by evaluating gene x environmental interactions*

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Parkinson's disease (PD) is a complex disease with no clear unifying etiology, but with defined pathological endpoints: α-syn accumulation and loss of dopamine neurons. Recent advances in genetics and epidemiology have identified dozens of genes and environmental factors tied to PD pathogenesis. However, genetic background and environmental exposure (exposome) do not occur in isolation. Indeed, many "PD genes" often display incomplete penetrance in their affected populations, suggesting they determine pathogenesis by interaction with one's environment. Given that α-syn accumulation is one of the hallmark features of disease, we will test complex gene-environment (GxE) interactions in a high throughput manner to see whether we can reverse engineer this feature of disease. By exposing neurons of different genetic backgrounds to a combined cocktail of environmental risk factors, I will determine which combinations elicit a PD-like phenotype using ELISA and high-content imaging to quantify and visualize α-syn. After highlighting which GxE combinations converge to elicit PD-like phenotypes in neurons, I will validate these in differential neuron populations, in dose- and time-dependent manners to gain a full appreciation of the molecular interplay. At the end of this project, we will have a newfound trove of data to help us better understand the pathogenesis of PD and therefore develop new targets for disease intervention.

P3-C-75: *A noise-driven spiking neural network model exhibiting seizure-like dynamics yields insights into the roles of neural heterogeneity, correlated input, and channelopathies in seizure onset*

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Despite seizures representing a gross departure from typical brain activity, predicting their onset is notoriously difficult. Computational models play a critical role in exploring putative mechanisms of how the brain can paroxysmally transition into seizure-like states, informing the development of therapies like neuromodulation. However, most existing models of seizure-like activity are deterministic with transitions triggered by predictable changes to a control parameter, impeding the exploration of this seemingly stochastic state transition. Here we present a novel spiking excitatory-inhibitory (E-I) neural network model with heterogeneous model neurons including physiologically-motivated spike-frequency adaptation and voltage homeostasis, which exhibits seizure-like activity driven by changes in the system's noisy input. The system transitions into seizure-like activity spontaneously and stochastically, with the frequency of seizure-like events driven by properties of the noisy input. We find that highly correlated noise elicits significantly more seizure-like events than non-correlated noise, indicating that overly homogeneous input represents a pathway by which seizure may be initiated or propagated. Furthermore, the system is more resilient to ictal-like transitions with

increased neural heterogeneity, both in single unit excitability and the contribution of Ih-like voltage homeostasis or Im-like spike-frequency adaptation. These results suggest that both input statistics and biophysical heterogeneity are important mechanisms that drive ictal-like transitions.

P3-C-76: *Patrolling monocytes promotes neurovascular repair in multifocal cerebral microangiopathies*

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Introduction Cerebrovascular dysfunction constitutes a key factor in the pathogenesis of vascular dementia (VaD). Multifocal cerebral microinfarcts (MCM) are small ischemic lesions associated with the obstruction of penetrating arterioles leading to neuronal loss associated with neuroinflammatory responses. Circulating monocytes respond to injury and contribute to tissue repair. However, the role of patrolling monocytes in the pathobiology and therapy of MCM remains unknown. Hypothesis, methods, and objectives We postulate here that patrolling monocytes play an essential role in maintaining neurovascular functions following MCM. For this purpose, we generated chimeric mice subjected to multifocal micro-occlusion and in which patrolling monocytes are either dysfunctional or functional but labelled to allow in vivo tracking in the brain. Furthermore, pharmacological approaches were used to stimulate patrolling monocyte production using muramyl dipeptide (MDP) systemic administration. Results Our findings indicate that patrolling monocytes transiently infiltrate the brain and are recruited to the microinfarcts one week after MCM. The depletion impaired microvascular integrity, exacerbated neuronal loss and aggravated cognitive decline. Importantly, stimulation of patrolling monocyte production using MDP strongly enhanced microvascular integrity and attenuated neuronal loss, while promoting cognitive functions. Conclusion Our findings suggest that patrolling monocytes play an important role in maintaining cerebrovascular functions following MCM and that pharmacological stimulation of patrolling monocytes constitutes an interesting approach to decelerate the cognitive decline associated with VaD and neurodegenerative disorders associated with vascular dysfunction.

P3-C-77: *Identification of Dickkopf-1 as a potent repressor of subacute repair and chronic recovery associated to with anxiety-like behavior upon stroke*

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Introduction Ischemic stroke constitutes a major cause of death and disability of the adult in Canada. We have previously demonstrated that stroke deregulates canonical Wnt pathway activity, which plays

key roles in regulating neurovascular functions. Interestingly, Dickkopf-1 (DKK1), an endogenous inhibitor of the pathway, has been shown to be induced after stroke, correlating with poor neurological outcomes. Yet, DKK1's implication in stroke pathobiology and therapy remains unknown. Hypothesis, Methods and Objectives Our study aims to elucidate the role of DKK1 after stroke. For this purpose, conditional mice allowing temporal induction of DKK1 subjected to ischemic stroke via middle cerebral artery occlusion (MCAo). Furthermore, pharmacological approaches were used to neutralize DKK1's biological activity as new therapeutic interventions to stimulate brain repair and recovery. Results Our findings indicate that DKK1 induction aggravated infarct and oedema sizes and aggravated motor functions after stroke. Moreover, DKK1 induction was accompanied by increased neuronal degeneration, while preventing neurogenesis, neuronal maturation, and angiogenesis. These changes were associated with an impaired neuroinflammatory responses. Interestingly, DKK1 prolonged chronic induction attenuated long-term structural restorative processes and functional recovery, associated with emergence of anxiety-like behavior. Finally, pharmacological neutralization of DKK1's biological activity using WAY262611 improved structural and functional recovery after stroke. Conclusion These findings indicate that DKK1 plays a central role in stroke pathobiology and its neutralization constitutes a clinically relevant approach to enhance structural and functional short and long-term recovery.

P3-C-78: *Enhanced output of VIP interneurons is followed by a deficit in hippocampal inhibition in behaving 3xTg-AD mice*

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Alzheimer's disease (AD) is characterized by a progressive memory loss associated with neuronal death in the hippocampus. The 3xTg-AD mouse model displays cognitive deficits as well as tau and β-amyloid neuropathologies essential for AD diagnosis. Although the hippocampus is affected in early stages of AD, how specific types of GABAergic interneurons (INs) - such as type 3 interneuron-specific (I-S3) cells - are affected, remains unknown. I-S3 cells express vasoactive intestinal peptide (VIP) and play an important role in memory formation as they gate the information arriving to the hippocampal CA1 region by providing disinhibition of principal excitatory cells. Here, we examined the morphological and electrophysiological properties of I-S3 cells in 6-month-old 3xTg-AD mice and the activity in their target oriens/alveus (O/A) INs while freely behaving. Our data showed no changes in the I-S3 cells' density and morphology in 3xTg-AD compared to non-transgenic mice. However, whole-cell patch-clamp recordings revealed an increase in the action potential half-width of I-S3 cells, and

the enhanced inhibition of their target - O/A INs - in 3xTg-AD mice. Using fiber photometry calcium imaging in freely behaving mice, we observed a decreased activity of CA1 O/A INs in 3xTg-AD animals during periods of quiet state, rearing and walking. Together, these data indicate that the enhanced I-S3 cells' output in 3xTg-AD mice may result in a decreased recruitment of CA1 INs. These changes could lead to hippocampal circuit hyperactivity and contribute to memory formation defects in AD.

P3-C-79: *Ketamine prevents sevoflurane-induced persistent memory deficits and a sustained increase in GABAA receptor function in mice*

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Sustained cognitive deficits after anesthesia and surgery are major health concerns. General anesthetic drugs, including sevoflurane, trigger a sustained increase in extrasynaptic GABAA receptor function, which may contribute to such cognitive deficits. Interestingly, ketamine, a dissociative anesthetic that primarily targets NMDA receptors, may be neuroprotective. The goals were to determine whether ketamine prevents sevoflurane-induced 1) persistent memory deficits in vivo and 2) sustained increase in GABAA receptor function in vitro. Adult C57BL/6 mice were anesthetized with sevoflurane (2.3%, 2 h) or exposed to medical air. Some mice were treated with ketamine (10 mg/kg, I.P.) or vehicle 30 min before the exposure. Recognition and spatial memory were studied after 24 h and 48 h, respectively. Cocultures of hippocampal neurons and cortical astrocytes were treated with sevoflurane (266 μM; 1 h) or vehicle with and without ketamine (10 μM). Extrasynaptic GABAA receptor function was studied 24 h later by recording whole-cell tonic current in neurons. The results showed that control mice demonstrated recognition and spatial memory, whereas sevoflurane-treated mice did not. Mice co-treated with ketamine regained recognition and spatial memory. Sevoflurane increased the amplitude of the tonic current and ketamine prevented this increase. In summary, ketamine prevented memory deficits and the persistent increase in GABAA receptor function after sevoflurane treatment. These studies identify a novel mechanism that may account for the cognition-sparing properties of ketamine.

P3-C-80: *Transcriptomic analysis reveals mitochondrial deficits in a mouse model of spinocerebellar ataxia type 6 (SCA6)*

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Spinocerebellar ataxia type 6 (SCA6) is a rare, late-onset disease, characterized by progressive ataxia and cerebellar degeneration. It is caused by an expansion of the CAG triplet repeat in the gene CACNA1A, which is highly expressed in the principle cell type in the cerebellum, Purkinje cells. How this expansion causes SCA6 pathophysiology is incompletely understood. We use a humanized mouse model with an expanded triplet repeat (SCA684Q/84Q) that recapitulates the late-onset and progressive nature of the human disease to study its pathophysiology. We performed RNA sequencing on SCA684Q/84Q and wildtype control animals at an age when motor deficit emerges, and identified over 500 significant differentially expressed genes in SCA6 compared to controls ($q<0.05$). We next conducted pathway enrichment analysis to gain insights into the biological processes represented by these genes, and identified novel pathways for SCA6, such as oxidative phosphorylation and mitochondrial proteins. To address whether mitochondria are affected in SCA6, we first examined their morphology, since morphological changes are a hallmark of defective mitochondria. Using transmission electron microscopy, we observed that mitochondria were swollen and majority of them showed signs of damages at advanced disease stage in SCA684Q/84Q Purkinje cells ($p<0.0001$). This work demonstrates for the first time the potential roles of mitochondria in SCA6 pathophysiology and suggests mitochondrial-targeting treatment as a prospective therapeutic avenue for SCA6.

P3-C-81: *Regulation of mechanical hypersensitivity and inflammatory pain by endogenous and exogenous amyloid-beta in the spinal dorsal horn*

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Synaptic plasticity that allows for memory in the brain has mechanistic and functional parallels to synaptic plasticity that occurs between neurons in the spinal dorsal horn. The small peptide, amyloid-beta (Aβ), is associated with memory loss in Alzheimer's disease and modulates synaptic plasticity towards synaptic depression. We hypothesize that Aβ contributes to synaptic plasticity and sensory processing in the spinal dorsal horn. We use central sensitization as a model for investigating synaptic plasticity in the spinal cord. To determine if Aβ plays a role in central sensitization we modulated endogenous levels of Aβ. We increased Aβ levels transiently via intrathecal injection of synthetic Aβ and decreased Aβ levels via a gamma-secretase inhibitor DAPT in wild type mice. We also used a knockout mouse model of the Aβ precursor protein (APP KO) which does not produce Aβ and an APP mouse model that over produces Aβ (TgCRND8). Mechanical sensitivity was tested by paw withdrawal threshold using Von Frey filaments. An inflammatory model of central sensitization mechanically sensitized wildtype animals but was not impacted by varying levels of Aβ via synthetic and DAPT injection. Interestingly APP KO mice did not respond with a change in mechanical sensitivity and in contrast TgCRND8 male mice did show improved mechanical sensitivity. A neuropathic model of central sensitization did show improvement in mechanical sensitivity after DAPT injection in both

sexes and after Aβ injection in females only. Future experiments will investigate potential mechanisms of how Aβ contributes to synaptic plasticity and sensory processing in the spinal cord by contrasting the molecular mechanisms of inflammatory and neuropathic models of central sensitization.

P3-C-82: *Loss of TBC1D7 causes behavioural and cognitive deficits in mice*

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Disruption of the mTORC1 pathway is a known cause of intellectual disability (ID). For instance, mutations in TSC1 and TSC2, which form a complex that negatively regulates mTORC1 activity, cause Tuberous Sclerosis, a disorder that is associated with ID, autism and epilepsy. TBC1D7, an essential component of the TSC1/TSC2 complex, also inhibits mTORC1 activity. We have previously shown that biallelic truncating mutations in TBC1D7 cause a form of ID that is characterized by the presence of behavioural abnormalities and megalencephaly. We hypothesized that the loss of TBC1D7 causes cognitive impairments by increasing mTORC1 signalling in cortical and hippocampal neurons. To investigate this hypothesis, we generated a Tbc1d7 null allele in mice via CRISPR by removing exons necessary for the interaction with TSC1/TSC2. The absence of TBC1D7 in mutant mice was confirmed by Western Blot. Tbc1d7 -/- mice are viable but display deficits in the marble burying, contextual fear conditioning and novel object recognition tests. These results suggest that Tbc1d7 plays a role in cognition and in normal interaction with the environment in mice. We are currently determining whether the loss of Tbc1d7 increases mTORC1 activity in the brain and affects the morphology of its neuronal circuits, as documented for other mTORopathies. We will also determine whether the administration of mTORC1 inhibitors can rescue the cognitive deficits of Tbc1d7 mutant mice.

P3-C-83: *Motor Impairment and Transcriptomics Profiling in Mice with a Gain-of-Function Mutation in the Retinoic Acid Receptor Beta (RARB)*

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Retinoic acid (RA) plays a critical role in the brain by binding to receptors that function as ligand-activated transcription factors. We previously found that de novo variants in the retinoic acid receptor beta gene (RARB) cause dystonia. Cell-based assays showed that these variants enhance RA-induced transcriptional activity, suggesting a gain-of-function (GOF) mechanism. As Rarb is predominantly expressed in the striatum during development and postnatally, we hypothesized that the dystonia of

patients with RARB GOF mutations is caused by increased RA signaling in the striatum. To investigate this hypothesis, we generated a mouse line with p.R394C, the equivalent of a GOF mutation found in 40% of patients. RarbR394C/R394C mice die perinatally whereas RarbR394C/+ mice survive into adulthood. Behavioral assessment showed a specific motor phenotype characterized by a short stride, increased activity in the open field, and reduced motor coordination in the rotarod and balanced beam paradigms. Moreover, RNA-seq studies showed that downregulated, but not upregulated genes, are significantly enriched for direct targets of RARB in the striatum of E18.5 RarbR394C/R394C and RarbR394C/+ embryos as well as P60 RarbR394C/+ mice, suggesting that p.R394C does not behave as a GOF but rather as a LOF allele in vivo. These studies also showed a decrease of several transcripts associated with dopamine signalling. Therefore, our results raise the possibility that pathogenic variants in RARB cause dystonia by disrupting RA and dopamine signaling in the striatum.

P3-C-84: *A novel peptide targets radixin to reduce activity of α5GABAA receptors in mice*

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Introduction Dysregulation of α5GABAA receptors (α5GABAARs) contributes to a variety of neurocognitive disorders. Exposure to general anesthetic drugs trigger a persistent increase in α5GABAAR activity that causes memory deficits. Various negative allosteric modulators have been developed to reduce α5GABAAR activity; however, none have proven to be effective in clinical trials. Thus, new treatment strategies are needed. Methods Hippocampal slices were prepared from mice aged 8-9 weeks. Slices were preincubated with okadaic acid to induce phosphorylation. Radixin-α5GABAAR binding was assessed using co-immunoprecipitation and western blots. In other studies, co-cultures of hippocampal neurons and cortical astrocytes prepared from embryonic mice were treated with etomidate or vehicle, with or without TAT-peptide or TAT-scrambled peptide for 1 h. Etomidate was washed away after 1 h, and the tonic current generated by GABA was recorded 24 h later. The α5GABAA receptor antagonist bicuculline was used to measure the amplitude of the tonic current. Results and conclusions Okadaic acid increased radixin-α5GABAAR binding, whereas the rho-kinase inhibitor Y-27632 reduced this binding. The peptide markedly reduced radixin-α5GABAAR binding. The tonic current generated by α5GABAARs was increased by etomidate, and its amplitude was reduced by the peptide, but not the scrambled peptide. Our results provide the first evidence of a novel strategy to reduce α5GABAAR activity by disrupting the binding of these receptors to radixin. This promising strategy may be helpful in developing treatments for disorders associated with over-activity of α5GABAARs.

P3-C-85: *Development and validation of a novel polygenic risk score indexing dendritic inhibition affected in depression*

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Reduced GABA somatostatin positive (SST+) interneuron-mediating dendritic inhibition may underlie lower cortical inhibition in depression. SST+ neuron transcriptomes are affected by age and these changes contribute to cognitive and mood-related behaviors. Accordingly, we hypothesized that a biological system related to SST+ neurons is affected in depression and contributes to the underlying causes and symptoms, such as cognitive impairment; and that a transcriptome-based genetic score capturing variability in this system can index risk for depression and its underlying symptoms in older adults. To test this hypothesis, we first identified genes associated with the cortical SST+ neuron system through postmortem gene co-expression analysis seeded by SST (n=210, ages 20-92), then identified genetic variants related to variability in these genes through cis-eQTL summary statistics (CommonMind Study), and aggregated them into a polygenic risk score (SST-PRS). SST-PRS was then calculated for each individual in a clinical sample of depressed older adults (IRL-GREY; n=393, 63% women, ages 60-90) and tested as a predictor for mood symptoms and cognitive function. SST-PRS was associated with more depressive symptoms ($p<0.03$), and better memory performance ($p=0.004$) in women; and with reduced language ability ($p=0.004$) in men. These preliminary results set the stage for developing an easily-accessible biomarker that indexes a well-characterized phenotype (reduced cortical inhibition) and predicts risk for depression and associated symptoms, to be validated in clinical populations.

P3-C-86: *Modifying RGMa-Neogenin recruitment Preserves Blood-brain Barrier Integrity Following Stroke*

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Stroke is associated with blood-brain barrier (BBB) compromise. The repulsive guidance molecule (RGM)-neogenin signaling pathway promotes stroke associated BBB leakage leading to reduced functional recovery, which can be mitigated by modifying RGM-neogenin interaction. C57B mice were subject to right middle cerebral artery occlusion. At 48 hours post-stroke mice were IV injected with fluorescent lysine-fixable dextran conjugated dye. An optical clearing procedure was applied to whole brains and the dextran distribution was mapped using light-sheet microscopy. We discovered the administration of two RGM pathway members, RGMa and Hfe2, can open and close the BBB, respectively. Our evidence indicates that either post-stroke Hfe2 administration or RGMa endothelial

receptor knockdown can mitigate stroke-induced BBB breakdown and significantly reduce behavioral deficits. Furthermore, blocking RGMa-neogenin interaction (transgenic RGMa point mutant) improved neuronal cell survival and reduced infarct volume. Several mechanisms contribute to post-stroke BBB breakdown. We investigated the post-stroke period where BBB leakage has been shown to be maximal, indicating that the RGMa and Hfe2 dependant mechanism is a major factor in stroke induced BBB leakage. Relatedly, patients suffering from liver diseases are more prone to intracerebral brain hemorrhagic events, potentially due to reduced BBB integrity. Using inducible liver-Hfe2 knock down in mice, we found that the liver is the likely source of Hfe2-mediated BBB protection, independent of stoke. Conclusion: Reducing stroke associated BBB leakage by modulating the RGM-neogenin signaling pathway led to improved functional recovery. This novel BBB protective mechanism likely has a liver-specific contribution.

P3-C-87: *Investigating neurodevelopmental and axonal defects in human models of the 15q13.3 microdeletion disorder*

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The 15q13.3 microdeletion syndrome is a highly penetrant copy number variant associated with epilepsy, autism spectrum disorder, schizophrenia, and intellectual disability. Our lab has previously identified a driver gene within the microdeletion, OTUD7A, and were able to identify its axon-rich proteomic network using a proximity proteomics screen in mouse cortical neurons. We have shifted to a human model using our extensive cohort of 15q13.3 patient-derived induced pluripotent stem cells (iPSCs) which are being used to examine cerebral and dorsal organoids at multiple time points across development. We hypothesize that these models will display early neurodevelopmental defects that later contribute to axonal and synaptic deficits in mature neurons. NGN2-induced neurons (iNs), cerebral organoids, and dorsal organoids were generated using our 15q13.3 iPSC cohort. iNs were assayed for early growth and axonal properties, and organoids were examined as single organoids or assembloids using light sheet microscopy. We identified accelerated growth in 15q13.3 cerebral organoids as well as increased NPC populations within rosette structures. Using 2D iNs, we found reductions in axon length and disrupted axon initial segments. To examine axonal innervation in a 3D context, dorsal assembloids have been generated and will be examined one-month post-innervation using light sheet microscopy. Our team has identified early developmental abnormalities in human models of the 15q13.3 microdeletion syndrome, including NPC proliferation and axon length. We are currently working to understand the molecular and cellular mechanisms that underlie these abnormalities to provide valuable insight into what may precede the late-stage neuronal deficits described in 15q13.3 patients.

P3-C-88: *Studying brain interferonopathies in human pluripotent stem cell-derived 3-D cultures*

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Aging and other neurological disorders are linked to the upregulation of the type I interferon (IFN) signaling pathway in the brain. Pathological signs of aged brains are also abnormally present in children who have inherited genetic variants that nullify IFN negative regulators: part of a group of disorders called interferonopathies. We hypothesize that, in interferonopathies, astrocytes and microglia become neurotoxic. We performed gene targeting--via CRISPR--of the interferonopathy allele interferon-stimulated gene 15 (ISG15) into pluripotent stem cells and we are differentiating them into the most abundant neuroglial components of the brain (neurons, astrocytes, and microglia). Taking advantage of tissue engineering, genetic reporters, and last-generation 3D cultures, we are modeling human ISG15-deficiency in the dish, to pinpoint cellular culprits of neuroglial impairment. Preliminary results show that ISG15-deficient astrocytes resemble reactive astrocytes, the latter also found in Alzheimer's and Parkinson's disease patients.

P3-C-89: *Platelet derived growth factor (PDGF)-D promotes neurovascular repair after stroke via stimulation of the pro-angiogenic properties of pericytes*

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Stroke is one of the leading causes of death and disability in the world. Brain pericytes are specialized multitasking cells that play a key role in generating critical neurovascular functions, including vascular stabilization and maintenance. Due to their multitasking properties, pericytes constitute a promising target for the development of new therapeutic interventions after stroke. We hypothesize that stimulation of the pro-angiogenic properties of pericytes attenuates stroke-associated damage. For this purpose, C57BL6 mice were subjected to ischemic stroke. Mice were treated in the subacute phase via the intranasal route with siRNA or recombinant active peptide of platelet-derived growth factor (PDGF)-D, a newly identified PDGF isoform that specifically activates PDGFRβ in pericytes to assess brain damage. Moreover, human primary brain pericytes exposed to ischemic-like conditions in vitro were used to decipher the mechanisms underlying role of PDGF-D effects. Our findings indicate that endogenous PDGF-D is transiently increased in the brain after stroke. Reduction of PDGF-D expression using siRNA delivered via the intranasal route exacerbated brain damage after stroke. The intranasal infusion of PDGF-D reduced brain atrophy and neuronal loss associated with stroke and increased the vascularization of the injured tissue. Interestingly, PDGF-D promoted the coverage

of pericytes at the lesion site via attenuation of apoptosis. These changes were accompanied by an improved neurological recovery. Our results suggest that PDGF-D plays an important role in promoting the pro-angiogenic functions of pericytes upon ischemic stroke. The overall results thus suggest that pericytes are an interesting target for the development of new therapies for stroke.

P3-C-90: *Constitutive nuclear accumulation of endogenous alpha-synuclein in mice causes motor dysfunction and cortical atrophy, independent of protein aggregation*

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Parkinson's disease (PD) is a neurodegenerative disorder characterized in part by the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of alpha synuclein (aSyn) throughout the brain. Although aSyn is natively found at the synapses and in the nucleus, there is a growing body of evidence that implicates the accumulation of nuclear aSyn plays in the pathogenesis of PD. To elucidate the functional consequences of constitutive nuclear aSyn in vivo, we engineered a novel mouse line (Snca-NLS) in which endogenous flag tagged aSyn is localized to the nucleus via a nuclear localization signal (NLS). The SncaNLS/NLS mice exhibit age-dependent motor deficits in rotarod, adhesive test, and beam break, together with altered gastrointestinal function and decreased survival. I observed motor cortex atrophy in the absence of midbrain dopaminergic neurodegeneration and aSyn pathology. I also sampled cortical proteomes of homozygous Snca-NLS mice and found several dysregulated proteins involved in dopamine signaling, including Darpp-32, Pde10a, and Gng7. These results suggest that constitutive nuclear aSyn can elicit toxic phenotypes in mice, independent of its aggregation. Importantly, the absence of these phenotypes in the Snca knockout mice suggests a neomorphic toxic function for aSyn in the nucleus. This model raises key questions related to the mechanism of aSyn toxicity in PD and provides a new model to study an underappreciated aspect of PD pathogenesis.

P3-C-91: *Using 3-dimensional human stem cell-derived cell cultures to model the impacts of microglia in Alzheimer's disease.*

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Alzheimer's disease (AD) is a progressive neurodegenerative disease that is the most common cause of dementia. There are currently no treatments that can stop or slow the progression of the disease.

Common to all AD patients is the accumulation and aggregation of neurotoxic amyloid-β in the brain parenchyma. Recent evidence also implicates microglia, the resident immune cells of the brain, in AD susceptibility. Mouse models indicate that amyloid deposition can be dependent upon glial-induced inflammation, and in human patients, inflammation is present at the early stages of AD. A remarkable number of genes specifically expressed in microglia have been highlighted in genome-wide association studies of AD, including membrane-spanning 4-domains A6A (MS4A6A) and MS4A7 whose functions remain largely uncharacterized. To better understand the role of microglia in AD pathogenesis, we have developed 2D and 3D neuro-immune cell culture models that integrate human pluripotent stem cell (hPSC)-derived microglia-like cells (MLCs) with amyloidogenic neural cells. We have found that exposure of MLCs to amyloid-β induces higher expression of inflammatory cytokines and chemokines. Additionally, we are using our cultures to evaluate the phenotypes of MLCs that lack expression of MS4A6A and MS4A7, and have found that MS4A7-/- MLCs are deficient in phagocytosis. These neuro-immune cell cultures will allow us to further dissect how microglia function within an amyloidogenic environment and can serve as a platform to study the functions of other genes associated with sporadic AD.

P3-C-92: *Assessing The Long-Term Effects of Microbe Therapy as Treatment for Depression*

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Many conventional psychiatric treatment methods, particularly antidepressant medications, are often accompanied by a high rate of relapse and illness reoccurrence following discontinuation of treatment. Given their unique influence on mood via the gut-brain axis (GBA), gut-repopulation techniques are now being explored as a possible treatment option for psychiatric illnesses such as depression and anxiety, due to their ability to repopulate the gut with bacteria from a healthy donor. However, given the novelty of using microbe therapy to treat psychiatric symptoms, the long-term effects regarding sustained improvements in mood are currently unclear. Microbial Ecosystem Therapeutic-II (MET-2) is a daily, orally-administered, microbial capsule that is currently being assessed for its use as treatment for depression. Approximately ten participants aged 18-45 who previously received MET-2 treatment will be recruited. Participants will return 12- and 24-weeks post-MET-2 treatment to assess for any lasting changes in mood using validated clinical scales and to provide a stool sample for microbial analysis using 16S rRNA sequencing. It is predicted that participants who previously received MET-2 are more likely to have a sustained improvement in mood at 12-weeks post-treatment than at 24-weeks post-treatment, based on existing literature. To date, four participants (n=4) have consented to participate in the study, however preliminary data on all enrolled participants will be reported and presented. Due to the limited studies that have assessed the longitudinal effects of microbe therapy on mood, any results from this follow-up will provide

valuable insight and be pivotal for evaluating the promise of gut-repopulation techniques as treatment for psychiatric illnesses.

P3-C-93: *The novel role of atfs-1 in promoting apoptosis in c. elegans models of Parkinson's disease*

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Parkinson's Disease (PD) is a neurodegenerative disease characterized by the progressive loss of dopaminergic neurons. Using primary dopaminergic neurons, we have previously determined that Activating Transcription Factor-4 (ATF4), a key regulator of the Integrated Stress Response (ISR) promotes apoptosis in vitro models of PD. In this study, we aimed to further characterize ATF4 mediated dopaminergic degeneration in vivo by studying the C. elegans ortholog atfs-1. C. elegans contain a simple nervous system and shortened lifespan, ideal for modelling age-related neurodegenerative phenotypes. To study the role of atfs-1 in experimental PD paradigms, atfs-1 loss-of-function (LoF) and gain-of-function (GoF) mutants were crossed with transgenic animals expressing human alpha-synuclein or treated with PD toxins. We have determined that atfs-1 promotes the transcriptional activation of apoptotic genes and subsequent caspase 3 activity in vivo. Using confocal microscopy, we have demonstrated that atfs-1 LoF animals are resistant to dopaminergic neuron loss which we have correlated to a conservation of dopamine-mediated basal slowing behaviour. Importantly, atfs-1 LoF animals have increased survival and extended lifespan as compared to wild-type animals in these experimental PD models. Our novel data recapitulating the role of ATF4 in vivo dopaminergic neuron loss and the important findings that atfs-1-deletion improves dopamine-mediated behaviour provides further evidence for targeting the ISR and ATF4 for the development of therapeutics to prevent neuronal apoptosis in PD.

P3-C-94: *Modelling Inflammatory Demyelination using Human Pluripotent Stem Cell-Derived Cultures*

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Demyelination is a state where the protective coating of neurons known as myelin is destroyed. Of all demyelinating disorders, the most prevalent is multiple sclerosis (MS), whose causes are largely unknown. We focus on a more deterministic monogenic demyelinating disease, X-linked

adrenoleukodystrophy (ALD), which affects 1 in 17,000 male infants. In cerebral ALD, a rapidly progressive inflammatory demyelination overtakes the brain and causes patient death in 2-3 years. This type of inflammation may also be in MS. In MS and ALD, myelin fails to regenerate, presenting a significant therapeutic challenge. Encouraging our efforts, myelin has the intrinsic ability to regenerate in healthy individuals, albeit inefficiently. Our focus is on the resident brain macrophages - microglia - as one of the driving factors causing demyelination, and failing to promote remyelination. Our lab uses human pluripotent stem cells (hPSCs) to engineer immuno-competent 3D avatars containing neurons, astrocytes, oligodendrocytes and transplanted microglia. In order to model inflammatory demyelination, we generated ALD mutant cell lines using CRISPR. Our study provides a platform to understand how inflammation underlies demyelination, and how microglia can be manipulated to promote recovery.

P3-C-95: *Longitudinal calcium imaging of the somatosensory cortex in awake mobile mice demonstrates a disruption in neural activity, network connectivity, and in the function of neural assemblies after stroke*

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Ischemic stroke leads to alterations in the balance of excitation/inhibition as cortical plasticity rewires lost connections and compensates for loss of function due to damaged tissue. Acute imaging preps with anesthetized animals have measured changes in sensory-evoked regional activity and neuronal response properties post-stroke. However, acute preparations do not allow for the tracking of cell populations across multiple imaging times during recovery and anesthetized preparations result in a lack of self-generated corollary signals occurring during awake behavior. Here we used two-photon calcium imaging of neurons in the limb-associated somatosensory cortex of GCaMP6S mice to define changes in network activity during awake movement within a mobile homecage. Peri-infarct neuron activity was measured weekly starting prior to stroke and for two months following photothrombotic stroke directed to the forelimb somatosensory cortex. Post-stroke behavioral deficits were measured weekly using the mobile homecage, as well as a tapered beam task and string-pulling task. Our data revealed a decrease in neuron activity, disrupted network functional connectivity and aberrant neural assembly architecture and function near the stroke border within the first week post-stroke. These changes were coincident with behavioral deficits on a tapered beam task at 1 week after stroke. Notably, disrupted neuronal and network properties returned to baseline levels as early as 2 weeks after stroke, suggesting potential for rapid plasticity of peri-infarct neural networks after photothrombotic stroke.

P3-C-96: *Sleep and autophagy as drivers of disease progression in Alzheimer's disease knock-in mouse models*

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Sleep disruption precedes Alzheimer's disease (AD) diagnosis, exacerbates proteostasis impairments and β-amyloid (Aβ) and tau pathologies, and greatly contributes to cognitive decline. Emerging evidence implicates autophagic dysfunction because of sleep loss in AD, with mounting Aβ and tau inducing sleep impairments; however, the mechanistic interplay remains elusive. We hypothesize that autophagy and sleep alterations occur concurrently and early in AD progression, driving neuropathologically-related cognitive decline. To test this, we will utilize the AppNL-G-FxMAPT double knock-in (dKI) AD mouse model (Aβ plaque, hyperphosphorylated tau neurites) compared to MAPT KI controls (no pathology) at ages representing early, moderate and advanced pathological states. Barnes maze and home-cage assessment (PhenoTyper) will test spatial memory/executive function and sleep behavior, with sleep stage time and transitions measured by EEG headcap recordings. Time-course EEG/EMG data has been accurately mapped to behaviour, matching neuronal frequencies with movement, sleep at baseline, during sleep-fragmentation and after recovery, and location in the Barnes maze. At the early-stage, no cognitive or home-cage deficits were detected in dKI mice. Finally, sleep-fragmentation induces tau hyperphosphorylation and impairs autophagy. Further immunohistochemistry is ongoing to determine vulnerable neuronal populations. Describing interactions of sleep loss with autophagic failure will elucidate contributions to cognitive decline, aiding in the design of novel treatments and biomarkers for AD.

P3-C-97: *Fatty acid metabolism dysregulations in the 5xFAD mouse model of Alzheimer's disease.*

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Metabolic abnormalities occur during aging, in both the body and brain and play a prominent role in Alzheimer's disease (AD). There is growing evidence pointing to peripheral and cerebral lipid metabolism dysregulations as potential targets to treat AD. In the present study, we use the 5xFAD model of AD to investigate the relationships between lipid metabolism, sex, genotype, and key hallmarks of the pathology throughout its development. Immunohistochemistry analyses showed advanced amyloid plaques deposition and microgliosis in 5xFAD males and females at 5 months of age, while Golgi-COX staining helped demonstrate the synaptic loss in the dentate gyrus and CA1 regions of the hippocampus. In addition, lipid energy metabolism increased with aging, and Gas Chromatography with Flame Ionization Detector (GC-FID) showed modified total fatty acid levels in

5xFAD mice. These findings are pointing to a pathogenic pathway in which fatty acid metabolism dysregulations are linked to the development of Alzheimer's disease and may represent a potential therapeutic target to treat it.

P3-C-98: *Cellular mechanisms of Thr175 tau phosphorylation in traumatic brain injury*

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Hyperphosphorylated tau protein is a primary hallmark of various neurodegenerative diseases, including Chronic traumatic encephalopathy and ALS-FTD. Tau phosphorylation at Thr175 (pThr175 tau) is an early marker associated with fibril formation, present in multiple tauopathies. Phosphorylation of Thr175 tau initiates a cellular cascade, which results in the activation of GSK3β, phosphorylation of Thr231 tau and fibril formation. However, it is currently unknown which kinase is responsible for the phosphorylation of Thr175 tau. This pathological cascade has been replicated in a rodent model of traumatic brain injury. We identified that the presence of pThr175 tau inclusions occurs within the first ten days following injury. The level of LRRK2, JNK1 and ERK1/2 is increased in traumatic brain injury rodents compared to non-injured controls within the first ten days, which temporally aligns with an increase of pThr175 tau and thus present as candidate kinases. To investigate the role of LRRK2 in the phosphorylation of Thr175 tau, HEK-293T cells were co-transfected with human WT-tau and one of three LRRK2 mutants: WT, G2019S (constitutively active) or 3XKD (inactive). There was no difference in the level of pThr175 tau, GSK3β activation and pThr231 tau in cells transfected with WT or G2019S-LRRK2 compared to 3XKD-LRRK2 or tau alone, suggesting that LRRK2 is not involved in this pathological process. Determining which kinase phosphorylates Thr175 tau is critical to further elucidate pathological tau-related mechanisms in CTE and identify potential therapeutic targets.

P3-C-99: *Chemogenetic inhibition of the ventral hippocampus reduces compulsive ethanol drinking in female rats on a novel ethanol two alternative forced choice task*

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Women develop alcohol use disorder (AUD) faster than men and display greater susceptibility to negative health consequences from drinking. Preclinical research suggests that females display more aversion-resistant drinking than males, both in paradigms that adulterate ethanol with quinine and in paradigms that co-deliver footshock with ethanol. Despite this, AUD remains more strongly associated

with, and studied in males, and much more is known about the neural basis of compulsive drinking in males. To enhance our understanding of the neural control over compulsive drinking in females, the current study employed a novel ethanol two alternative forced choice task in which adult female Long-Evans rats were trained to choose between two levers that delivered low ethanol reward, or high ethanol reward accompanied by increasing levels of shock (0.07-0.49mA). The point of subjective equality (PSE), the shock level where both options are valued equally was quantified as the primary variable of interest. The ventral hippocampus (vHPC) was chemogenetically inactivated in rats transfected with inhibitory DREADDs (using clozapine-N-oxide, 3mg/kg) while they performed free choice trials with the two lever ethanol options. We found that vHPC inhibition reduced PSEs and led to lower ethanol consumption compared to within-subject (saline), and between-subject (GFP) controls, particularly at the shock levels closest to the PSE. Our data implicate the engagement of vHPC in compulsive forms of ethanol choice and drinking in females.

P3-C-100: *Systemic delivery of SNCA gene silencers reduces enteric alpha-synuclein*

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Parkinson's disease (PD) is characterized by the misfolding of alpha-synuclein (a-syn, encoded by SNCA) into toxic oligomers which can spread between neurons in a prion-like mechanism. The motor symptoms of PD occur after a significant loss of nigrostriatal dopaminergic neurons. Clinically, however, a significant number of PD patients develop gastrointestinal (GI) symptoms many years before their motor deficits manifest. The finding of a-syn in the GI tract and the recent characterization of a body-first model of PD suggest that synucleinopathy may begin in the GI tract, and implicate enteric a-syn as a possible target for enteric PD therapeutics. Here, we test whether systemically delivered SNCA silencers can reduce enteric a-syn in mice and delay the gut-to-brain spread of synucleinopathy. Mice expressing human wild-type synuclein received intravenous injections of AAV9-SNCA-shRNA or a scrambled control (AAV9-scr-shRNA) tagged with turboGFP. In a previous study in our lab, the shRNA was delivered to the brain via focused ultrasound and showed significant reduction of a-syn in the targeted regions. TurboGFP immunostaining of the GI tract confirmed that leftover shRNA is expressed in enteric neurons while western blot quantification revealed a trend towards decreased a-syn in the stomach but not in the colon. Future experiments will test the prophylactic ability of enteric a-syn knockdown in mice that will receive synucleinopathy triggers in the GI tract. These can potentially translate to a novel, non-invasive, and relatively compliable neuroprotective agent for PD.

3D. Sensory and Motor Systems

P3-D-101: *Probing the timescales of perception with white noise optogenetic inhibition*

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During visually guided behaviours, mere hundreds of milliseconds can elapse between a sensory input and its associated behavioural response. How spikes occurring at different times and in different sensory brain areas are read out to generate perception and action remains poorly understood. To explore temporal relationships between sensory input, perception, and behaviour, we delivered random pulse trains of optogenetic stimulation (white noise) to excite inhibitory interneurons in either the primary visual cortex (V1) or superior colliculus (SC) of mice while they performed a visual detection task. We then used a reverse correlation analysis on the optogenetic stimuli to generate a neuronal-behavioural kernel: an unbiased, temporally-precise estimate of how suppression of V1 or SC spiking at different moments during a behavioural trial affects detection of that visual stimuli. Electrophysiological recordings enabled us to capture the effects of optogenetic stimuli on V1 responsivity and revealed that only the earliest stimulus-evoked spikes (~50 ms) in SC and V1 are heavily weighted for guiding behaviour. Ongoing experiments are aimed at determining whether spike weighting dynamics differ between SC and V1 depending on the identity of the visual stimulus (e.g., luminance versus contrast). These data demonstrate that white noise optogenetic stimulation is a powerful tool for understanding how patterns of spiking in neuronal populations are decoded in generating perception and action.

P3-D-102: *Sexual dimorphism in beclin 1 regulation of mechanical hypersensitivity in inflammatory and neuropathic pain*

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Chronic pain affects approximately 20% of the population. Autophagy is a ubiquitous cellular process and dysfunctional autophagy has been implicated in many neuropathologies, however whether autophagy is involved in pain processing is unclear. Here, we aimed to determine whether autophagy regulates pain sensitivity by specifically targeting a key protein in autophagy machinery, beclin 1 (Becn1). Mice with peripheral inflammation or peripheral nerve injury (PNI) are hypersensitive to mechanical stimuli. In an inflammatory pain model where mice receive intraplantar complete Freund's adjuvant (CFA), mice lacking one allele of Becn1 (Becn1+/-) show greater mechanical hypersensitivity

compared to Becn1+/+ mice, but only in males, not in females. Administrating a becn1-activating peptide (tat-becn1) intrathecally reversed CFA-induced mechanical hypersensitivity in wild-type mice to a greater extent in males than females. Tat-becn1 also reversed PNI-induced mechanical hypersensitivity in males only. In pain states, the GluN2B subunit of the NMDA receptor is upregulated in neurons in the spinal dorsal horn - the initial pain processing site of the central nervous system - leading to hypersensitivity. We found that naïve Becn1+/- mice have increased expression of GluN2B in the dorsal horn compared to Becn1+/+ mice, while females showed no difference. In sum, we found that Becn1 regulates inflammatory and neuropathic pain hypersensitivity in a sex-specific manner. We further suggest this may occur through Becn1 regulation of GluN2B expression.

P3-D-103: *Activity patterns of sympathetic preganglionic neurons during fictive locomotion in the in-vitro neonatal mouse spinal cord*

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Spinal cord injury (SCI) is a devastating life altering event, with lost movement and impaired body functions caused by loss of communication between the brain and spinal cord. Electrical stimulation of lumbar spinal cord has emerged as a powerful intervention for people with SCI as clinical trials have shown its ability to improve both movement and restore lost autonomic body functions (e.g., BP regulation). Although promising, neural mechanisms mediating observed recoveries using this intervention remain unknown. We hypothesize that ascending neurons from lumbar regions give input to thoracic sympathetic preganglionic neurons (SPNs) that in turn, provide homeostatic support for movement. Our lab has recently shown that lumbar locomotor-related neurons synapse on SPNs throughout the thoracic spinal cord. Thus, we have begun characterizing activity patterns of SPNs before and during fictive locomotion in the in-vitro neonatal mouse spinal cord. We recorded lumbar ventral root (VR) activity and imaged fluorescent signals from SPNs (pre-loaded with calcium dye) on the cut surface of thoracic spinal cord (T6 - T11). Our preliminary data indicate varying numbers of SPNs active at baseline, which may be correlated with spontaneous VR discharge. With the appearance of tonic and/or rhythmic locomotor activity, additional distinct SPNs become active, suggesting that there may be a functionally integrated relationship between SPNs and locomotor circuits. Experiments specifically activating or inhibiting defined neural paths between lumbar locomotor and thoracic SPNs are ongoing.

P3-D-104: *Heightened response to noxious cues following development in a noxious environment*

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All nervous systems need to reliably transform sensory information into appropriate motor outputs that generate coordinated actions. Such actions do not arise de novo, but change over the course of development. The neural mechanisms underlying this adaptation, however, remain unclear. Here, we use nocifensive behaviour in Drosophila larvae as a model to study the neural mechanisms underlying developmental adaptation to a noxious environment. We see that chronic exposure to noxious cues leads to a hypersensitivity to noxious input, behavioural changes comprising a lower nociceptive threshold, an early detection of noxious cues, a delayed termination of nocifensive behaviour and lack of habituation to the cue. This behavioural phenotype is affected by factors, most notable being the frequency of nociceptive stimulations, and may be observed across all nociceptive modalities. This change in behaviour is sustained by signalling through octopamine signalling at the sensory level, with knock-down of octopamine receptors preventing sensitization but sparing optogenetically-induced nocifensive behaviour. Briefly, this research provides a better understanding of the mechanisms underlying experience-dependent changes in the nociceptive system of one of the most powerful animal models for studying genetics. This, in turn, may open new avenues of research on adaptive and maladaptive changes in nociceptive systems in general, shedding new light into the mechanisms underlying acute and chronic pain.

P3-D-105: *The persistent effects of sports-related concussion during adolescence on sensorimotor integration*

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A history of concussion increases the risk of subsequent musculoskeletal injury. The increased risk may reflect persistent alterations in sensorimotor control during periods of high cognitive demand. The current study used short-latency afferent inhibition (SAI) to probe differences in two sensorimotor circuits, known to be sensitive to cognitive load, in a cohort of individuals with and without a history of concussion. SAI was quantified in the first dorsal interosseous muscle (FDI) during a cued finger response task using either posterior-anterior current for 120 μs (PA120) or anterior-posterior current for 30 μs (AP30). Preliminary findings suggest that concussion history decreases FDI SAI in the PA120 sensorimotor circuit compared to the no history group during validly cued index finger responses. Yet, both groups demonstrate a similar decrease in SAI in response to an invalid cue requiring a non-index finger response. In contrast, both groups demonstrate similar levels of AP30 SAI during validly cued index finger responses. However, there is a marked decrease in AP30 SAI following an invalid cue for those with a concussion history. The present results suggest a general decrease in sensorimotor circuits sensitive to executive load (PA120) following concussion. In contrast,

sensorimotor circuits sensitive to perceptual demands (AP30) are abnormally engaged during periods of high perceptual load. Following a concussion, persistent alterations in sensorimotor integration may reflect the compensatory allocation of perceptual and executive resources.

P3-D-106: *Delayed motor learning in a 16p11.2 deletion mouse model of autism is rescued by locus coeruleus activation*

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Children with autism spectrum disorder often exhibit delays in achieving motor developmental milestones such as crawling, walking and speech articulation. However, little is known about the neural mechanisms underlying motor-related deficits. Here, we reveal that mice with a syntenic deletion of the chromosome 16p11.2, a common copy number variation associated with autism spectrum disorder, also exhibit delayed motor learning without showing gross motor deficits. Using in vivo two-photon imaging in awake mice, we find that layer 2/3 excitatory neurons in the motor cortex of adult male 16p11.2-deletion mice show abnormally high activity during the initial phase of learning, and the process of learning-induced spine reorganization is prolonged. Pharmacogenetic activation of locus coeruleus noradrenergic neurons was sufficient to rescue the circuit deficits and the delayed motor learning in these mice. Our results unveil an unanticipated role of noradrenergic neuromodulation in improving the delayed motor learning in 16p11.2-deletion male mice.

P3-D-107: *Profiling the sensory epithelium of the human balance organ and using a damage paradigm in sensory hair cell regeneration*

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The human balance organ, utricle, is comprised of a mosaic of sensory hair cells, responsible for detection of movement, and supporting cells. Loss of sensory hair cells due to aging leads to permanent balance deficits affecting 6 million Canadians. Since supporting cells survive, they represent an excellent target population for endogenous regeneration. We used single-cell RNA-sequencing (scRNA-seq) to elucidate supporting cell heterogeneity in utricles from patients with acoustic neuroma. We identified, for the first time, 6 putative types of supporting cells.

Characterization of the different supporting cells is a first step towards identifying which subtype(s) represent 'stem' cells for hair cell regeneration. To assess human utricle's genes and transcription factors that are involved in the damage and potential regenerative response, we used a gentamicin hair cell damage paradigm. We damaged, in culture, utricles from the same cohort of patients and evaluated the early response to damage as this might represent a critical time window to set the stage for HCs regeneration. After 24 h, we isolated the RNA from the sensory epithelia and performed bulk and scRNA-seq in control and gentamicin-treated samples. We discovered human-specific genes and identified the earliest response to damage, paving the way for developing therapeutics for the treatment of balance dysfunction.

P3-D-108: *Mechanoreceptor and innervation density in marmoset hands*

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Mechanoreceptors are specialized structures that respond to the stresses and strains in the skin that arise when it is deformed. In the glabrous skin of the hand, Aβ afferent fibers branch extensively before innervating multiple low threshold mechanoreceptors (Meissner corpuscles, Merkel complexes), leading to complex receptive fields. Recent studies have shown that these first order Aβ afferent fibers signal fine details of touched objects, suggesting the complex innervation constitutes a peripheral neural mechanism for extracting the spatial features of touched objects and surfaces. In the present work, we have established an approach for determining the density of low threshold mechanoreceptors and the morphology of their innervation in marmoset hands using immunohistochemistry and confocal imaging. We present the difference in mechanoreceptor and innervation densities across different regions of the marmoset hand. This work provides a baseline of the peripheral morphology in marmosets and will facilitate the study of the changes occurring in the periphery after nerve injury.

P3-D-109: *Optogenetic targeting of preBötzinger Complex GABA and glutamate cells depresses breathing in mice*

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Breathing is controlled by the rhythmic activity of brainstem breathing centers to generate respiratory rhythms. The preBötzinger Complex (preBötC) is involved in inspiration and our lab has shown that activation of the preBötC glutamate neurons increases respiratory rate. The preBötC has a

heterogeneous cell population and half of the neurons in the preBötC are inhibitory, but the role of preBötC γ-aminobutyric acid (GABA) neurons in breathing are unknown. To activate preBötC GABA neurons, we expressed channelrhodopsin in cells expressing the vesicular GABA transporter (vGAT). We then recorded diaphragm and genioglossal muscle activities in anesthetized mice and used focused 470 nm light to stimulate preBötC vGAT cells. We injected fentanyl (5µg/kg) and activated vGAT cells following baseline respiratory recordings. We performed similar experiments while inhibiting glutamate neurons (554 nm focused light) by expressing the inhibitory archaerhodopsin in vesicular glutamate transporter 2 (vGlut2) cells to validate the role of glutamate in respiratory rhythms. Our preliminary data indicate that vGLUT2 inhibition and vGAT excitation blocks inspiration. Determining the role of GABA and glutamate preBötC cells in coordinating respiratory rhythms will allow us to better understand what is occurring in the brain when breathing is depressed such as in opioid-induced respiratory depression. By identifying the cells involved in respiratory depression by opioids, we may be able to develop new and safer analgesics that do not target these sensitive breathing areas.

P3-D-110: *Eye movement-dependent and independent processing related to face perception.*

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The human visual system is highly developed for detecting visual objects, with faces being particularly salient and important objects. Scanning faces with our gaze (i.e. 'free viewing') is thought to be important for our ability to learn new faces, as well as for our facility to recognize familiar ones. Specifically, gaze-tracking research has shown that we tend to make stereotyped eye movements when viewing faces, focusing our gaze on 'internal' facial structures including the eyes, nose and mouth. However, there are significant disagreements in the field regarding whether people use 'holistic' or 'analytic' strategies to learn and recognize faces (i.e. if faces are processed as a whole or as a set of individual features). We hypothesize that contradictory results arise because most studies to date used faces small enough to be learned or recognized without absolutely requiring eye movements. We thus set out to specifically examine the effect of varying face size on recognition, in both free viewing and fixation conditions. Interestingly, for both viewing conditions, we find that humans are able to recognize familiar faces over a very large range of sizes (roughly 1-100 degrees in height) and that eye movements only become absolutely required for recognition of very large faces. Furthermore, although eye movements provided no significant advantage over fixation for faces 1-100 degrees in height, participants maintained a stereotyped gaze pattern when free viewing these faces. These results provide insights in eye movement-dependent and independent forms of face perception.

P3-D-111: *The role of inhibitory neurons in the brainstem circuit mediating optokinetic reflex*

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Inhibition is critical for information encoding and processing by neural circuits. Although the roles of inhibition in the visual cortex are well understood, much less is known about how it is involved in visual processing in the brainstem. To fill this knowledge gap, we chose to study a brainstem complex consisting of the nucleus of the optic tract and the dorsal terminal nucleus (NOT-DTN), which mediates horizontal optokinetic reflex (OKR), an imaging stabilization mechanism. GABAergic inhibitory neurons are abundant in this structure, but their roles are yet to be determined. First, by using optogenetic assisted identification methods, we showed that these inhibitory neurons are more heterogeneous in preferred directions and exhibited less direction-selective than excitatory neurons in the NOT-DTN. They also preferred lower spatial frequencies, compared to the excitatory neurons. Second, with electrophysiology and anatomical tracing, we found that in NOT-DTN inhibitory neurons projecting to the superior colliculus and the one projecting to the MTN came from two non-overlapping populations with distinct direction and spatial frequency tuning curves. Finally, optogenetic activation of NOT-DTN inhibitory neurons sharpened the tuning curves of excitatory neurons and enhanced their selectivity to visual features; while silencing these inhibitory neurons gave rise to the opposite effects. Our results indicate that the inhibitory neurons play an important role in shaping visual feature selectivity of brainstem circuits.

P3-D-112: *Investigating the intrinsic noisiness of cortical sensory processing*

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Persistent spontaneous activity interacts with task-evoked activity to provide a net neuronal response. These rest-stimulus interactions are observed in primary sensory cortices and modulate processing of elicited sensory input. The nature in which spontaneous cortical activity interacts with sensory-evoked responses is complex and is demonstrated to play significant role in observed trial-to-trial variability, or 'noisiness'. We used C57BL/6J-Tg GP4.3Dkim/J transgenic mice expressing the calcium indicator, GCaMP6s, in cortical pyramidal neurons to explore the intrinsic noisiness of elicited cortical responses induced by different sensory stimuli under the anesthetized and awake states, including visual, auditory, and somatosensory stimulation using a transcranial, mesoscale, neuroimaging paradigm. We investigated the input-output and signal-to-noise ratio (SNR) relationships of sensory-evoked responses in primary sensory cortices. Differences were observed in the duration of sensory-

evoked responses among different sensory domains under anaesthesia and wakefulness. Despite not exhibiting appreciable differences in mean response amplitude, different sensory domains showed different signal-to-noise ratios with the relation to sensory input under anaesthetized and awake states. Elucidating rest-stimulus interactions are essential to our understanding of sensory processing and may have implications to our understanding sensory abnormalities described in neuropsychiatric disease contexts.

P3-D-113: *High resolution mapping of muscle coordination in rat frontoparietal cortex with intracortical microstimulation (ICMS) paired with electromyography (EMG)*

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Most motor cortex (M1) mapping experiments have focused on a primary muscle or joint involved in stimulation evoked movements. Such studies thus do not account for the complex patterns of muscle coactivation driving natural behaviour or the naturalistic movements we and others have evoked with long-train ICMS like reaching, feeding, and defensive movements. Here we describe mapping of rat frontoparietal cortex with traditional kinematic analysis combined with EMG collection, which provides superior temporal and anatomical resolution of evoked muscle coactivations. We applied long (500 ms) and short train (50 ms) ICMS to M1 and surrounding fields in anesthetized rats while recording video and EMG from multiple muscles. A novel closed-loop system controlled the stimulation timing and parameters using EMG feedback. This system recognizes spontaneous movements common under light anesthesia and pauses the stimulation sequence to avoid recording corrupted data. EMG-based maps for each muscle were visualized automatically via a custom Voronoi map generator in MATLAB. For ongoing experiments, we are using a new system for semi-real-time EMG analysis which significantly improves brain mapping efficiency. This suite of methodological improvements will enable us and other groups to make large, high-resolution motor maps of cortical muscle coordination. High-density EMG-based maps reveal the muscles involved in a complex movement as well as their sequence of action. This makes it possible to map numerous muscle coordination and timing patterns.

P3-D-114: *Express Visuomotor Response in upper limb can select targets within 90ms of visual stimulus onset*

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In time-sensitive situations, humans rely on orienting reflexes which allow them to move rapidly in response to sudden visual events. These reflexes are generated through subcortical processing of visual stimuli. The Express Visuomotor Response (EVR) is an orienting reflex presenting as a brief burst of muscle recruitment which we hypothesize originates in the superior colliculus (SC). The EVR shares characteristics with express saccades, a well-studied orienting reflex. Both responses are spatially and temporally locked to the visual stimuli. Likewise, express saccades and EVRs occur preferentially in response to stimuli with lower spatial frequencies. In this study, we investigate if EVRs shared another characteristic of express saccades: preference for faces. Subjects were asked to reach towards one of two simultaneously appearing targets: a face symbol and a scrambled face symbol presented randomly on the left or right of fixation. The instruction as to which symbol to move towards varied over alternating blocks. Muscle activity in the pectoralis major muscle of the reaching arm was recorded using skin surface EMGs. We found that an EVR reflecting muscle activation occurred within 90ms independent of instructed target. The EVR, however, occurred more rapidly and reached a higher amplitude in response to the instructed target. This demonstrates that the EVR can be modified by top-down modulation to identify stimulus features.

P3-D-115: *On the role of mu-opioid receptors in respiratory depression and locomotor hyperactivity by the opioid fentanyl*

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Opioid drugs bind to mu-opioid receptors (MORs) and can exert both inhibitory effects, leading to respiratory depression (a severe decline in breathing rate), and excitatory effects, characterized by locomotor hyperactivity in rodents. Here, we aimed to characterize the dual effects of the opioid fentanyl on breathing and behaviour. We hypothesized that fentanyl induces respiratory depression combined with a simultaneous increase in locomotor activity by acting on MORs. In situ hybridization was used to map MOR mRNA expression in brainstem regions involved in breathing or behaviours. Respiratory depression and motor hyperactivity were induced by an intraperitoneal injection of fentanyl (0.3mg/kg) in male wildtype and MOR knockout (MOR-/-) mice. Respiratory rate was recorded using whole-body plethysmography and video recordings were captured to assess behaviour. We found that MORs were expressed in multiple brainstem regions involved in breathing or behaviours. We also found that fentanyl injection induced a significant respiratory rate depression in wildtype mice ($P<0.0001$, $n = 8$), while no such change was observed in MOR-/- mice ($P=0.9833$, $n=7$). Similarly, fentanyl injection increased locomotor activity in wildtype mice but not in MOR-/- mice. We conclude that MORs are expressed in brainstem respiratory and locomotor regions and that fentanyl induces its effects on breathing and behaviours by acting on MORs. Funding: research support was provided

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P3-D-116: *Whole-brain dynamics and state transitions underlying spontaneous behavior in larval zebrafish*

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Simultaneous whole-brain imaging and behavioral experiments in larval zebrafish have started to reveal how distributed neuronal networks interact to generate a wide array of behaviors. While most studies have focused on neural mechanisms behind stimulus-evoked behavior, we ask how internal brain states and neuromodulation generate spontaneous motor events. Using volumetric resonant two-photon microscopy, we measure whole-brain neuronal activity in head-restrained transgenic zebrafish larvae expressing pan-neuronal nucleic calcium indicators, while monitoring tail movements using a high-speed camera. A screen is used to alternate sequences of light and dark, driving motor output during the experiment. Clustering algorithms reveal multiple spontaneous swim types which vary in kinematic properties and temporal organization. Using regression, tail movement clusters are associated with spatially distributed neuronal populations which are correlated to movement on various time scales, suggesting distinct roles in generating and encoding behavior. To investigate the large-scale functional background of this specialized motor activity, we decompose brain dynamics into a sequence of recurrent states of regional activity using clustering. These brain states exhibit modular spatial organization and transition probabilities which are similar across individuals. By incorporating the molecular information of immunolabelings and open-access gene expression markers, we will study how neuromodulators drive these internal state transitions to influence behavior.

P3-D-117: *Chemogenetic activation of glutamatergic preBötzinger Complex neurons increases breathing in mice*

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Objective: Respiratory rhythm is largely regulated within the medulla, with the preBötzinger Complex (preBötC) critical for inspiration. The preBötC contains a heterogenous group of neurons, with a large portion being glutamatergic and marked by vesicular glutamate transporter 2 (vGLUT2). A subpopulation of preBötC neurons co-express μ-opioid receptors, lending to its role in opioid-induced

respiratory depression. We propose that activation of vGLUT2-expressing preBötC neurons can stimulate respiration and potentially alleviate opioid-induced respiratory depression. Hypothesis: Glutamatergic preBötC neuron activation induces respiration in mice. Methods: Excitatory hM3Dq receptors were expressed in vGLUT2 preBötC neurons of vglut2-IRES-Cre male mice (Jackson Labs) through cre-lox recombination. Four weeks after insertion, mice were anesthetized and electrodes were implanted into the diaphragm and genioglossus muscles to record respiratory activity. Mice were given consecutive intramuscular injections of saline and the hM3Dq ligand, clozapine-N-oxide (CNO; 0.5 mg/kg), while respiratory responses were monitored. Following recordings, brains were collected for histological analysis. hM3Dq expression was determined through mCherry fluorescence. Results: CNO injection led to a 115.5% increase in respiratory rate 46-50 min following injection. There was an associated 42.6% decrease in diaphragm amplitude. Histology confirmed expression of mCherry in the region of the preBötC. Conclusions: Preliminary data showed that respiratory rate can be increased through glutamatergic preBötC stimulation during anesthetized conditions. Further studies will determine if stimulation of glutamatergic preBötC neurons is sufficient to overcome opioid-induced respiratory depression.

3E. Homeostatic and Neuroendocrine Systems

P3-E-118: *Maternal high-fat diet and neonatal lipopolysaccharide exposure potentiates inflammatory microglial morphology and gene expression*

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Inflammatory stress in early life, including maternal high-fat diet (mHFD) and neonatal lipopolysaccharide (nLPS) exposure, have been found to predispose adult rodents to increased densities of microglia, the main immune cells in the brain involved in inflammation, and neuroinflammatory gene expression. These alterations have been associated with increased anxiety phenotypes and are a proposed mechanism for increased rates of psychiatric disorders found in humans with a history of maternal obesity and neonatal infection. However, it remains unknown the causes of the observed elevations in microglial densities and neuroinflammation. Using an immunohistochemical approach, the aim of this study was to delineate microglial activation states in hippocampal and amygdala subregions in adult rats exposed to mHFD and/or nLPS, at baseline and after a peripheral LPS challenge. We found that independent mHFD and nLPS exposures in females and males led to reduced resting morphology of microglia, increased activated morphology, and heightened colocalization with inflammatory activation markers including cluster of differentiation 68 and toll-like receptor 4. A similar finding was observed in females exposed to both mHFD+nLPS,

however a surprising finding was that males with a combination of these early life stressors displayed normalized effects. As aberrant microglial activity in the brain has been implicated in various neuropsychiatric disorders, our findings suggest that maternal obesity and neonatal infection may be a predisposition factor to the etiology of related pathologies.

P3-E-119: *Tipping the motivational scale: The role of AgRP neurons in ghrelin-driven feeding and foraging*

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A growing body of literature suggests that ghrelin not only increases hunger, but also initiates a spectrum of feeding-related responses. This pleiotropy makes sense from an adaptive perspective: foraging requires both increased motivational drive and suppression of fear of potential threats. The exact mechanism by which ghrelin alters these motivational states, however, has yet to be fully elucidated. We hypothesized that these effects are realized through ghrelin's actions on agouti-related peptide (AgRP) neurons of the arcuate nucleus. To test this, we used the novelty suppressed feeding test to determine if exogenous ghrelin injected peripherally would facilitate approach to a palatable snack, and to see if Melanotan II (MTII), a synthetic analogue of α-melanocyte-stimulating hormone, would block these effects. Intraperitoneal injections of either 0.1cc MTII and 0.1cc saline, MTII and 0.2cc ghrelin, saline and ghrelin, or saline and saline, were given to four separate groups of mice (n=18/group). 30 Minutes post-injection, we recorded the latency to approach food and amount of food eaten for a period of 10 minutes. Our results show that ghrelin shortened the latency to approach and increased total food intake. In contrast, mice treated with MTII and ghrelin consumed less food than those treated with ghrelin alone, but spent slightly more time eating and less time in corners than those treated with MTII alone. These findings suggest that ghrelin acts on AgRP neurons to suppress negative affective states associated with a novel environment and facilitate foraging and food intake.

P3-E-120: *A lateral head impact model for mouse studies on hypothalamic dysfunction associated with traumatic brain injury.*

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Objective: The development of central autonomic and endocrine dysfunction after traumatic brain injury (TBI) is believed to involve hypothalamic injury, but the underlying mechanisms are unknown. We developed a model of lateral head injury to study TBI-related dysautonomias in mice. Methods: Mice were lightly anesthetized with isoflurane and subjected to TBI using a Gothenburg Impactor (Collision Analysis Inc). This instrument was used to deliver a reproducible, calibrated blow to the side of the head of mice via a 50 g projectile launched at predetermined velocities (v). Mice treated the same way, but without the head impact served as controls (shams). Results: TBI caused increased righting times proportional to impact velocity, from 20 s at v = 5 m/s to 400 s at v = 11 m/s. This procedure typically did not cause any external lesion or bleeding. Up to v = 10 m/s, no mortality or skull fracture was observed and grimace scale measured 2 hours following TBI was 0. Mice displayed a transient (2-3 days) decrease in body weight of less than 10%. We examined cFos expression by immunohistochemistry in the supraoptic (SON) and paraventricular nuclei (PVN), key structures involved in diverse functions, including osmoregulation, autonomic control, energy metabolism and thermoregulation. Our analysis revealed marked activation of cFos in both SON and PVN as well as other hypothalamic nuclei. Conclusion: This model may be useful for studies on hypothalamic dysfunction associated with TBI.

P3-E-121: *Bisphenol A and bisphenol S effects on rapid estradiol- and stress-sensitive signalling mechanisms in the murine hippocampus*

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Bisphenol A (BPA) is an endocrine disrupting chemical that disturbs mechanisms of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes. Specifically, BPA dysregulates many estradiol- and glucocorticoid-sensitive non-classical signalling mechanisms that have rapid effects on cognition, synaptogenesis, and protein synthesis in the mammalian hippocampus (HPC). Therefore, many manufacturing processes replaced BPA with chemical analogues like bisphenol S (BPS). We aimed to investigate the effects of BPA and BPS exposure on rapid signalling mechanisms and neuroinflammatory protein markers within the murine HPC. Gonadally intact adult male and female CD-1 mice were treated with vehicle, BPA, or BPS-containing peanut butter at 50 µg/kg/day for 10 days. HPC protein lysates were analyzed for ERK, JNK, Akt, MKP3, GFAP, IBA-1, and PSD-95 expression. Our findings show that HPC MKP3 (phosphatase implicated in female-specific anxiety and depression) was significantly lower in BPA- and BPS-treated females. In vitro, female-derived HPC neurons were treated with 1, 10, 100, or 1000 nm of BPA or BPS in estradiol-free media for 1hr. Intriguingly, in vitro findings show that MKP3 expression was significantly increased by BPA in the absence of circulating estradiol. Collectively, these findings further our understanding of sexually differentiated cellular mechanisms of BPA and BPS in the mammalian HPC. Ongoing studies aim to further characterize sex

differences in the effects of bisphenols on anxiety, memory, dendritic structure, and non-genomic HPC signalling mechanisms.

P3-E-122: *Role of endogenous androgens in regulating pain-induced inflammation within the hippocampus and medial prefrontal cortex*

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Painful stimuli can raise glucocorticoid levels and propagate neuroinflammation which can negatively impact the hippocampus (HC) and medial prefrontal cortex (mPFC), two regions critical for learning and memory. Androgens display anti-inflammatory and neuroprotective effects such as inhibiting pro-inflammatory cytokine synthesis and restoring dendritic spines. Pain-induced inflammation can suppress endogenous androgens which may contribute to impairments in neuronal structure and function. However, the role of circulating androgen levels in attenuating pain-induced neuroinflammation within the HC and mPFC remains unclear. First, adult male Sprague-Dawley rats received a hind footpad injection of saline or complete Freund's adjuvant (CFA) to induce inflammatory pain. On day-7, the Von Frey filament test was used to determine the presence of allodynia. However, CFA-injected rats displayed no changes compared to controls. At 10-days, CFA-injected rats had a slight increase in serum corticosterone, while serum testosterone appeared to have recovered back to control levels. While the recovery of serum testosterone may have attenuated the development of allodynia, there appear to be lasting effects on HC morphology. CFA injection resulted in a decrease in CA3 dendritic branching and length in a dose-dependent manner. Ongoing experiments aim to investigate the early stress and inflammatory responses and how adrenal androgens modulate CFA-induced neuroinflammation. This work provides insights into the mechanisms mediating androgen regulation of neuroinflammatory responses.

P3-E-123: *Effects of long-term 5α-androstane-3α,17β-diol treatment on object recognition memory in the 3xTg mouse model of Alzheimer's disease*

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Age-related declines in circulating gonadal steroid hormones have been linked to the development of Alzheimer's disease (AD). Women have a greater risk of developing AD and suffer greater cognitive impairments than men, a sex difference that may be due, in part, to the neuroprotective effects of

androgens. Previous work by our group has shown that the neurosteroid metabolite of testosterone, 5α-androstane-3α,17β-diol (3α-diol), may be involved in protecting the brain against the development of AD-related cognitive dysfunction and pathogenesis. At 9 months of age, long-term object recognition memory (ORM) was significantly improved in 3α-diol treated 3xTg-AD mice, compared to untreated animals. Here, we investigated the effects of longer-term 3α-diol treatment in 12-month-old 3xTg-AD mice, when neuropathological and cognitive impairments are more fully developed. Male and female wildtype B6129SF2/J and 3xTg-AD mice received subcutaneous Silastic capsules filled with 3α-diol dipropionate between 3 and 12 months of age, at which time ORM and open-field behaviours were assessed. 3α-diol treatment significantly improved long-term ORM in male but not female 3xTg-AD mice. These data suggest that long-term 3α-diol administration may be protective against cognitive decline in 3xTg-AD males. Ongoing experiments investigate the effects of 3α-diol on dendritic morphology and AD-related neuropathology, and further elucidate the role of 3α-diol in AD-related pathogenesis.

3F. Cognition and Behavior

P3-F-124: *Investigating the interaction between D2-type dopamine receptors in the dorsal hippocampus and progesterone in social learning in male mice*

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Social learning is one of the most common and adaptive types of learning. It may be defined as "learning that occurs via the observation of, or interaction with, a conspecific or its products" (Heyes, 1994; Galef, 1998), and may be studied by utilizing the social transmission of food preference (STFP). The STFP has implicated the dopaminergic system, the dorsal hippocampus (HPC), estrogens, and androgens in social learning. In ovariectomized female mice, my preliminary findings suggest that progesterone reversed the impairing effects of intra-HPC D2-type dopamine receptor antagonism on social learning. It is unknown whether the same mechanisms are at play in male mice. Notably, in male and female mice, PR immunoreactivity was prominent in the CA1 region of the HPC, and PR were distributed similarly in both neurons and glia in the HPC formation (Mitterling et al., 2011). The present study aims to understand whether, like in females, dorsal HPC D2-type DA receptors interplay with progesterone receptors in the mediation of social learning in male mice. To test this, we implant subcutaneous slow releasing progesterone pellets, or vehicle pellets, in castrated "observer" (OBS) mice 10 days prior to infusing the D2-type DA receptor antagonist raclopride (20 μg/μL) into the dorsal HPC. Ten minutes after the infusions, OBSs undergo a 30-minute social interaction with a same-sex, familiar, recently fed "demonstrator" (DEM), followed by an 8-hour OBS choice test where OBSs have

free access to 2 novel flavored food diets. If social learning occurs, OBSs prefer the DEM diet. It is predicted that progesterone treatment will counter the impairing effects of intra-HPC D2-type DA receptor antagonism on social learning in castrated male mice. Funded by NSERC.

P3-F-125: *Estrogens in the medial Prefrontal Cortex of ovariectomized female mice rapidly facilitate social recognition but not object recognition*

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Estrogens rapidly facilitate short-term working memories in mice in various social and non-social behavioural tasks, in regions critical for memory formation, such as dorsal hippocampus (DH). Medial Prefrontal Cortex (mPFC), also an important region for memory, receives intensive estrogenic projections from DH and has high estrogen receptors expression. Additionally, estrogens in mPFC of female mice are necessary for the consolidation of objection recognition (OR) and object placement (OP) memory. However, whether estrogens in mPFC rapidly affect short-term memory remains unknown. Here, adult ovariectomized female mice were infused bilaterally in mPFC with either vehicle or one of the three doses (25, 50, 100μM) of 17β-estradiol (E2), then tested 15-min post-infusion in either social recognition (SR) or object recognition (OR) short-term memory tasks, both 'difficult', with control ovariectomized mice showing no SR and no OR. Results showed that E2 in mPFC rapidly facilitated SR but not OR short-term memory, suggesting a possible specificity of E2's rapid action in mPFC, for social cognition. Thus , one additional social cognition task using 'difficult' social transmission of food preferences paradigm (STFP), and one additional non-social cognition task using 'difficult' object placement paradigm (OP) are being tested. Altogether, this study helps probe estrogens' role on rapid short-term memory facilitation in mPFC of female mice and determine whether they prioritizes social over non-social cognition.

P3-F-126: *Gene-environment interactions exacerbate altered ultrasonic vocalization syntax in a rat model for neurodevelopmental disorders*

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Deficits in social communication and language development belong to the earliest diagnostic criteria of autism spectrum disorders (ASDs). Of the many risk factors for ASD, the contactin-associated protein-like 2 gene, CNTNAP2, is thought to be important for language development. The present study aimed to investigate potential compounding effects of ASD risk gene mutation and

environmental challenges, including breeding conditions or maternal immune activation (MIA) during pregnancy, on early vocal communication in the offspring. Maternal isolation-induced ultrasonic vocalizations (USVs) from Cntnap2 wildtype (WT) and knockout (KO) rats at selected postnatal days were analyzed for their acoustic, temporal, and syntax characteristics. Cntnap2 KO pups from heterozygous breeding showed normal numbers and largely similar temporal structures of USVs to WT controls, whereas both parameters were affected in homozygously bred KOs. Homozygous breeding further exacerbated altered call pitch and transitioning between call types found in Cntnap2 KO pups from heterozygous breedings. In contrast, the effect of MIA on the offspring's vocal communication was confined to call type syntax, but left USV acoustic and temporal organization mostly intact. Our results support the "double-hit hypothesis" of ASD risk gene-environment interactions and emphasize complex features of vocal communication as a useful tool for identifying early autistic-like abnormalities in rodent models of ASD. This study was supported by CIHR, NSERC, and the Deutsche Forschungsgemeinschaft (DFG) - project number 442662585.

P3-F-127: *Cannabis Use Among Canadian University Students: Differences across Gender and Mental Health Status*

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Cannabis is a commonly used substance in Canada, particularly among young adults. National cannabis surveys show that males and females differ in their patterns and reasons for cannabis use, but several studies have linked cannabis use to poorer mental health. Few studies, however, have assessed these variables among a university student population, a population that is considered vulnerable for the development of mental health disorders. The current study was conducted to identify differences in cannabis use by gender and mental health status among a sample of Canadian undergraduate students. We conducted an online survey of undergraduate students at Carleton University, Ottawa, Canada (N = 744) to explore patterns, methods, and reasons for cannabis use by gender and mental health status. A greater proportion of males were found to use daily/almost daily, use dried cannabis products, use alone, and were more likely to have problematic cannabis use. In contrast, more females reported monthly use, using cannabis edibles, and using with others. Students with a mental health disorder were more likely to report lifetime and problematic use, earlier age of first use, using alone and using before sleep. An earlier age of first use and multimodal use were also associated with cannabis use disorder symptomology. Current data provides insight on the methods, patterns, and reasons for cannabis use among a multicultural Canadian undergraduate student sample and illustrates key differences by gender and mental health status. These insights provide a

basis for future research and education/intervention efforts for the improvement of mental health outcomes in post-secondary students.

P3-F-128: *A Novel Role for the Lateral Hypothalamus Hypocretin/Orexin Neurons in Social Behaviour*

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Social behaviour and communication are essential for the survival of social animals; however, the neural mechanisms underlying these phenomena remain to be fully understood. The profound impact of social interaction on the survival of social organisms coupled with our incomplete understanding of the neural substrates underlying these processes make it important to unravel the neural basis of social behaviours. To undertake this objective, we examined the lateral hypothalamus (LH) that is implicated in the regulation of motivated and defensive behaviours. a. We hypothesized that the LH hypocretin (Hcrt; orexin) neurons which are critical for arousal and motivation, are an integral part of the brain's social systems. To test this, we used a novel Hcrt-Cre mouse model in a series of experiments designed to examine the function and specificity of Hcrt neuron activity during social behaviour. We performed fiber photometry to examine Hcrt neuron activity during social interactions with familiar and novel conspecifics in different settings. Here, we show that the activity of the Hcrt neuron population increases in response to interaction with conspecifics, and that this increase is significantly greater for novel conspecifics than familiar ones. Moreover, the optogenetic inhibition of Hcrt neurons diminishes time spent interacting with novel conspecifics. Overall, our data show that Hcrt neuron activity is integral to social interaction processes.

P3-F-129: *Intermittent versus continuous access to optogenetic stimulation of ventral tegmental area neurons produces greater motivation to self-stimulate*

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Animal models of drug addiction typically involve self-administration sessions where drug access is continuous. However, compared to continuous access (ContA), intermittent Access (IntA) to drugs more closely models the temporal pattern of human drug taking and it also promotes addiction-relevant changes in brain and behaviour. Thus, the temporal kinetics of drug-taking could be decisive in producing the neuroplasticity that underlies addictive behaviors. Here we asked whether greater responsiveness to intermittent vs. continuous reward intake is a fundamental property of the reward system, extending beyond drugs of abuse. We compared the effects of IntA versus ContA to

optogenetic stimulation of ventral tegmental area (VTA) neurons. Male Sprague Dawley rats trained to lever press for optogenetic self-stimulation of channelrhodopsin-expressing VTA neurons (3 sec, 10 mW, 20 Hz) received 12 sessions of Continuous (1hr) or Intermittent (5min ON, 5 min OFF for 1hr) access to VTA laser stimulation paired with a light and tone cue. After these 12 sessions, IntA rats achieved higher breakpoints for VTA laser stimulation under a progressive ratio schedule of laser reinforcement, greater resistance to increasing delays in laser delivery and greater operant responding for the laser-paired cue. Thus, intermittent activation of VTA neurons recapitulates some of the effects of intermittent drug intake and promotes increased reward seeking.

P3-F-130: *Local network architecture in children with mild traumatic brain injury*

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Background: Attention problems are common sequelae of concussion in children. Short superficial white matter (SWM) fibers in the brain are particularly vulnerable to concussion in children due to their protracted myelination and location at the grey-white matter interface. Objective: To describe alterations in the SWM in children with concussion, their impact on network community and attention. Methods: Children (9-10 years) with concussion (N=324) were matched to children without concussion (N=339) from the Adolescent Brain Cognitive Development Study. Particle filtering tractography was applied to multishell diffusion weighted MRI data to generate matrices weighted by fractional anisotropy (FA), fiber density (AFD) and fiber orientations (NuFO). SWM was derived via length thresholding (<85mm), while measures of local community (modularity, mean clustering coefficient (mCC)) were calculated from matrices not thresholded by length. Attention was assessed with the CBCL attention problem scale. Results: Linear mixed effects models indicated that children with concussion had more clinically significant attention syndrome scores (p=4.9x10-6). Concussed children had elevated FA (p=2.0x10-16), AFD (p=4.9x10-8) and NuFO (p=2.3x10-16) in SWM and lower modularity (p=2.0x10-16) and mCC (p=2.0x10-16) compared to controls. Interactions between FA (p=0.002) and NUFO (p=0.03) and age showed that in younger concussed children lower values were associated with better attention. Conclusions: Maturation of SWM fibers may be altered by concussion and impair attention.

P3-F-131: *Impact of a perinatal Mediterranean-based diet on mouse postpartum behaviour*

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About 17% of women worldwide suffer from postpartum mental illness, affecting postnatal interactions with the offspring and potentially their later-life mental health. Studies have shown that diet quality during pregnancy could influence the risk of postpartum depression and anxiety. This study examined, in a mouse model, the effects of a perinatal dietary intervention based on the human Mediterranean diet on postpartum behaviours. C57BL/6N female mice were fed with a Regular Chow (Control diet 1), Purified diet (Control diet 2), or a Med-based diet (Control diet 2 enriched with olive and fish oils, fruits, vegetables, legumes, and walnuts) and mated with males on identical diets after two weeks. On Postnatal Day 8 and 9, dams' behaviours were assessed using the Elevated plus maze, Open field, Splash, and Tail suspension tests. Compared to the Regular Chow control group, mice on the Med-based diet spent more time in the open arms and less time in the closed arms of the Elevated plus maze, indicating a reduced fear of open spaces, reminiscent of anxiety-like behaviour. The Med-based group also spent more time grooming and engaged in more grooming sessions than both control groups in the Splash test, indicating increased motivation to engage in self-care behaviours, reminiscent of depressive-like behaviour. Behaviours in the Open field and Tail suspension tests were not different between groups. These findings suggest that dietary modifications based on the Mediterranean diet during pregnancy may support maternal postpartum mental health.

P3-F-132: *Effects of early life inflammatory stressors on ultrasonic vocalization characteristics of rat pups*

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Rodent pups can emit ultrasonic vocalizations (USVs) to gain maternal care and increase survival chances. Previous studies have shown that inflammatory stressors in early life, including maternal high fat diet exposure and neonatal infections alter the number of USVs in rodent pups, as well as impact maternal care behaviour leading to long-term alterations in the offspring's stress physiology. However, there is limited work on the types of acoustic calls, based on their sonographic structure, that are being altered. To address this limitation, we examined the effects of maternal high-fat diet and neonatal infection exposures on post-natal day (PND) 7 Long-Evans rat pup USV emission. Using Deep Squeak, a machine learning system that has been recently developed for detecting and classifying rodent USVs, we are exploring the effects of early life stress on cluster waveform, and syntax of emitted USVs. This work can provide insight into how independent and combined exposures to early life inflammatory stressors can impact rat pup USV emission to inform changes in maternal care seeking behaviours.

P3-F-133: *mTORC1-mediated acquisition of reward-related place activity in hippocampal somatostatin interneurons during virtual reality spatial learning in head-fixed mice.*

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Long-term synaptic plasticity of principal cells is an essential substrate for hippocampal learning and memory, but the contribution of inhibitory interneuron plasticity remains ill-defined. Previous work showed that, in somatostatin interneurons (SOM-INs), bidirectional modulation of mTORC1 activity, a crucial translational control mechanism in synaptic plasticity, causes parallel changes in learning-induced long-term potentiation (LTP) in SOM-INs and hippocampus-dependent memory. These results suggest that SOM-IN plasticity regulate hippocampal networks and memory. To examine the changes in SOM-IN activity (global and synaptic), and their behavioral correlates, induced by learning, we used in vivo two-photon Ca2 imaging from SOM-INs in head-fixed mice during a virtual-reality spatial memory task, combined with cell-specific knockout of Raptor (SOM-Raptor-KO) in mice to block mTORC1 activity in SOM-INs. Our results show that SOM-Raptor-KO exhibits a learning deficit compared to control in the virtual reality spatial task. This behavioral deficit was also reflected in the Ca2 activity of SOM-INs. Control SOM-INs acquire over time spatial activity related to reward localization that was deficient in Som-Raptor KO. These spatial cellular activities can be classified into 4 types of spatial coding and can be remodeled after reward relocation. Our results suggest that SOM-INs develop mTORC1-mediated spatial coding related to reward localization learning. This coding could modulate and be used by pyramidal cells to represent and consolidate reward location. Funding: CIHR, CRC, FRQS

P3-F-134: *Sex-specific protective effects of the APOE ε2 allele on cognitive decline*

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The APOE ε2 allele protects against cognitive decline and Alzheimer's disease. APOE ε2 may have sex-specific effects on cognition. We investigated sex differences in associations between APOE ε2 and longitudinal cognitive decline in the National Alzheimer's Coordinating Centre (NACC) database. We included participants who were ≥50 years old, White, cognitively normal at baseline, and had at least one follow-up assessment. We grouped participants as APOE ε2 carriers or APOE ε3 homozygote carriers. APOE ε4 carriers (including ε2/ε4) were excluded. Cognition was assessed approximately annually. We examined the interaction between APOE allele (ε2 vs ε3), sex, and time on longitudinal

cognition in linear mixed models, controlling for baseline age, education, NACC test version, vascular comorbidities, and their interactions with time. N=6,819 participants were included (mean age=72.9±9.13 years, mean education=16.0±2.87 years, 62% female). There were significant interactions between sex, APOE allele, and time on longitudinal memory (β=0.024, p=0.023) and language (β=0.014, p=0.045), but not attention (β=0.009, p=0.179) or executive function (β=0.006, p=0.398). In sex-stratified analyses, male APOE ε2 (vs ε3) carriers showed slower decline in memory and language domains. Cognitive trajectories did not differ between female APOE ε2 and ε3 carriers. Among cognitively normal older adults, the APOE ε2 allele protects males but not females against memory and language decline. Sex-specific effects of APOE ε2 may contribute to the lower incidence of Alzheimer's disease observed in males.

P3-F-135: *Temporal dynamics of neuronal excitability in the lateral amygdala mediates allocation to an engram supporting conditioned fear memory*

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Memories are encoded by ensembles of neurons (engrams) that are active during learning. Neurons important in an engram (engram cells) are sparsely distributed across the brain. Within a given brain region, eligible neurons compete for allocation to an engram and neurons with increased excitability at the time of training are biased to be allocated to an engram. Previous findings show that neurons with increased excitability during training also have increased excitability for ~6 h. Because of this, two separate but similar training episodes within a 6 h time period tend to be co-allocated to a similar population of neurons and remembered together. Here we examined the temporal dynamics of neuronal excitability important for allocation to an engram. We focused on the lateral amygdala (LA) and cued fear memory. We expressed both an excitatory and inhibitory opsin in the same sparse, random subset of LA neurons. At different times before fear conditioning, we optically activated this sparse subset of neurons to allocate them to the engram. To examine whether these neurons were indeed critical components of the engram, we tested mice both in the absence of light and with optical stimulation to inhibit this same population of neurons. We find that optogenetic stimulation of neurons up to 6 h, but not 12 h or 24 h, before training biases their allocation to the engram. These findings indicate that excitability in the LA is temporally defined and plays a critical role in neuronal selection to a fear engram.

P3-F-136: *Optogenetic stimulation of the central nucleus of the amygdala intensifies and narrows incentive salience for laser-paired opioid and sucrose sensory rewards*

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The central amygdala (CeA) is a striatal-like structure implicated in directing motivation onto particular targets. Here we ask whether paired optogenetic stimulation of CeA amplifies and focuses motivation for intravenous opioid rewards. We trained rats to choose between two identical infusions of i.v. Remifentanil, but only one infusion was paired with CeA laser stimulation. Rats intensely pursued laser-paired Remi while ignoring the otherwise identical Remi option not accompanied by CeA stimulation. We then asked if CeA activation could similarly bias motivation when rats are choosing between two different sensory rewards. We trained rats to nose poke for sucrose, and separately, to nose poke into a different poke for i.v. Remi. For half of the rats, sucrose was paired with CeA activation, and for the other half, i.v. Remi was paired with CeA stimulation. Sucrose + laser rats exclusively responded for sucrose in lieu of Remi, while Remi + Laser rats overwhelmingly responded for Remi, ignoring the sucrose option. Finally, we study how CeA dopamine D1R and CRF expressing neurons mediate incentive motivation. Our results suggest that CRF and separately, D1R neurons in CA both narrow 'wanting' not matched by increases in 'liking' for reward. Our results suggest a role for CeA related circuitry in focusing an addiction-like desire for sensory rewards and help inform our understanding of the neural components that characterize irrational pursuit of drug rewards during cases of opioid addiction.

P3-F-137: *Perioperative neurocognitive disorders: a systematic review of preclinical studies*

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INTRODUCTION: The contribution of general anesthetic drugs to perioperative neurocognitive disorders is controversial. Due to the multiple confounding factors in clinical studies (e.g. surgical trauma), preclinical studies are needed to determine whether general anesthetic drugs cause persistent effects on cognition. A systematic review of preclinical studies was conducted to determine whether general anesthetic drugs cause cognitive deficits that persist after the drugs are eliminated from the brain. METHODS: MEDLINE was searched from inception to Dec. 31, 2021. Studies involving adult vertebrate animals that underwent a single exposure to a general anesthetic drug were included. The primary outcome was cognitive performance as evidenced by behavioural tests performed after recovery from general anesthesia (>24 hours) compared to non-exposed controls. Descriptive statistics were performed. RESULTS: All studies used rodent models (n=380). 75% of studies reported deficits in one or more cognitive domains; subgroup analyses identified age (86% vs 63% deficit in older and younger adult animals, respectively) and surgery (80% of studies found deficits

with surgery but not general anesthesia alone) as contributing factors, but not the choice of anesthetic drug. Memory was more frequently impaired than motor or anxiety-related behaviours. CONCLUSION: General anesthetic drugs were associated with cognitive deficits in most preclinical studies; age and surgery may increase risk. Further investigation will clarify the relationship and inform the design of future clinical trials.

P3-F-138: *Role of Lateral Habenula neural outputs in reward seeking behaviors*

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The brain reward circuit has a central role in reinforcing rewarding behaviors and preventing behaviors that lead to punishment (or the absence of reward). The lateral habenula (LHb) is positioned to control reward-seeking behaviors since it receives neural inputs from the limbic system and the basal ganglia, and in turn sends efferent projections controlling the dopaminergic ventral tegmental area and the serotoninergic dorsal raphe nucleus (DRN). Here, to examine the role of DRN-projecting LHb neurons in reward behavior, we use an intersectional viral approach to direct expression of the genetically encoded calcium sensor GCaMP6s in DRN-projecting LHb neurons to monitor their activity using fiber photometry calcium imaging in freely moving mice engaged in a probabilistic reversal reward task. In this task, mice normally select the most recently awarded choice to adapt its effort to maximize rewards consumption in light of reward expectations. Our hypothesis is that DRN-projecting LHb neuronal population play a role in reward processing and behavior control. Our results show that activity at DRN-projecting LHb neurons significantly increase at the onset of a trial, when the conditioned stimulus is presented (light), and return to baseline at the reward port entry. Surprisingly, this LHb neural output does not encode reward value. Taken together, these findings suggest that LHb neural outputs might be involved in conditioned stimulus encoding, particularly where there is uncertainty in reward expectation.

P3-F-139: *Trait impulsivity and sensation seeking on mesolimbic activity in the context of a monetary reward task*

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Trait impulsivity and sensation seeking are associated with abnormalities of the mesolimbic dopaminergic projections of the ventral tegmental area (VTA). The current study examines the

relationship between trait impulsivity and sensation seeking with VTA reactivity to reward and punishment cues. A total of 155 adolescents (aged 12 to 14 at study entry) were assessed at three time points over a five year period. Trait impulsivity and sensation seeking were assessed using the substance use risk profile scale. Differences in VTA activation were assessed using functional magnetic resonance imaging in the context of a monetary incentive delay task (MIDT). In the context of trait impulsivity, our results showed a significant within-person increase in VTA activity following an expected reward cue (B=20.117, SD=9.283, p=0.015), a significant decrease in activity following a loss avoidance cue (B=-0.173, SD=0.075, p=0.015) and a missed reward opportunity cue (B=-5.976, SD=2.555, p=0.011). Our analyses did not show any significant sensation seeking dependent changes in MIDT-related VTA activation. Our results suggest that differences in ventral tegmental reactivity may explain the difference between youths with high impulsivity and high sensation seeking personality profiles. This skewed mesolimbic reactivity may distort an individual's ability to learn and adjust their behavior based on external feedback.

P3-F-140: *The impact of gestational exposure to cannabinoids on memory capacity in adolescent and adult Sprague Dawley rats*

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The major cannabinoids in Cannabis (THC, CBD) interact with the human endocannabinoid system, which plays a role in memory. Cannabis is one of the most regularly used mind-altering substances during pregnancy; however, the effects of use on offspring memory are poorly characterized. To examine this we exposed pregnant Sprague Dawley rats to cannabinoids via injection (3mg/kg THC or 10mg/kg CBD) or smoke-inhalation (high-THC or high-CBD Cannabis flower) from gestational day 6 to 20. Behavioral testing of the pups occurred on postnatal day (PND) 30 for adolescents or PND 60 for adults. A novel odour recognition (NOR) task was used to test memory. The NOR task relies on the rat's innate preference for novelty to distinguish between novel and familiar odours. Two variations of this task were used; the identical odour task (IOT) which requires discrimination of two odours and the differential odour task (DOT) which requires discrimination of six odours. In adolescence, all treatment groups showed a preference for the novel odour in the IOT indicating intact working memory; however, only the control rats showed a preference for the novel odour in the DOT indicating rats exposed to cannabinoids during gestation were impaired in the higher memory capacity task. Data gathered from this experiment indicates gestational exposure to Cannabis impairs working memory capacity in adolescent offspring; however, further testing with additional rats is required to verify this. The adult data is being analyzed to determine if impairments seen in adolescence are maintained later in development.

P3-F-141: *Context matters: How do task demands modulate the recruitment of sensorimotor information during language processing?*

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Grounded theories of semantic representation propose that simulations of sensorimotor experience contribute to language processing. This can be seen in the body-object interaction effect (BOI; how easily a word's referent can be interacted with by the human body). Words with high BOI ratings (e.g., chair) are processed more quickly than words with low BOI ratings (e.g., cloud), and this effect can be modulated by how the task decision is framed. When asked to decide if a word is an object (entity condition), a BOI effect is observed, but when asked to decide if a word is an action (action condition), there is no BOI effect. It is unclear whether the lack of effect in the action condition reflects a top-down modulation of task-relevant sensorimotor information or the absence of bottom-up activation of sensorimotor simulations. We investigated this question using EEG. Fifty participants were randomly assigned to the entity or action condition and the same stimuli were used for both conditions: 100 entity words (50 high BOI and 50 low BOI) and 100 action words. In both conditions we observed differences in ERP components related to the BOI effect. In the entity condition the P2 mean amplitude was significantly more positive for high compared to low BOI words. In the action condition the N400 peak latency was significantly later for high compared to low BOI words. Our findings suggest that BOI information is generated bottom-up regardless of task demands and modulated by top-down processes that recruit sensorimotor information relevant to the task decision.

P3-F-142: *Coordinated activity between head direction cells in the thalamus and the medial entorhinal cortex*

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Flexible navigation requires signals that are updated irrespective of the external conditions. The demonstration that pairwise coordination of both grid and head-direction (HD) cells is maintained during sleep when external inputs are largely reduced, has provided experimental evidence for attractor dynamics in these systems. Specifically, this was shown separately for the HD cells of the anterodorsal nucleus (ADN) of the thalamus and for HD and grid cells of the medial entorhinal cortex (MEC). Inactivation studies previously showed that ADN HD cells are necessary for normal grid cell activity, begging the question of the exact role of the thalamic HD cells in MEC population activity. To address this problem, we performed simultaneous recording of thalamic HD cells and the MEC.

Methods: We implanted 32-channel and 32 or 64-channel probes into ADn and MEC respectively. The recordings consisted of a 2h sleep session, 30 mins exploration, followed by another 2h sleep session. Results: We analyzed 35 pairs of ADN-MEC HD cells. The coordination of ADN-MEC HD cell pairs was preserved during all phases of sleep, NREM and REM, the angular offset of the preferred direction during wake predicting the correlation during sleep, Conclusions: Our findings suggest that the HD signal is coherent across multiple areas of the brain's navigation system across all brain states. As ADN certainly exerts more influence on its cortical targets than it is itself influenced by cortical feedback, it is thus possible that the attractor dynamics observed in the MEC are inherited from upstream coherent activity.

P3-F-143: *Effects of chronic corticosterone treatment on behavioural phenotypes in C57BL/6 mice.*

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Introduction: Stress contributes to major psychiatric disorders like depression and anxiety. Under stress, corticosterone (CORT) is secreted by the adrenal cortex in rodents. This study aimed to access the behavioural changes of male C57BL/6 mice under a model of anxiety/depressive-like state induced by chronic corticosterone treatment. Methods: Thirty-one male C57BL/6 mice (8 - 17 weeks old) received CORT (35 µg/ml) or Vehicle (β-cyclodextrin 4.5 mg/ml) provided in drinking water over four weeks as previously described (David et al. 2009). To explore whether Fluoxetine (18 mg/kg/day) was able to reverse the anxiety/depressive-like state, after four weeks of corticosterone treatment, mice received CORT + Fluoxetine (18 mg/kg/day) or CORT + Vehicle for five weeks (Mendez-David et al., 2017). Anxiety-like behavior, locomotor activity, depressive phenotype, well-being, and mechanical sensitivity were investigated by the open-field arena, forced swimming test, cage hanging behavior, and von Frey filaments. CORT, IL-1β, and TNF-α levels were assessed in plasma. Results/Conclusion: After five weeks, the body weight increased significantly in the CORT group compared with Vehicle ($p=0.02$). The CORT group displayed a significant increase in immobility time on weeks 4 ($p=0.04$) and 8 ($p=0.0021$) compatible with depression states. CORT treatment seems not to impair locomotion functions in the open-field arena. An increase of paw mechanical sensitivity was seen in the CORT group on weeks 1 ($p = 0.0413$),5 ($p =0.0002$), and 9 ($p=0.0077$). Fluoxetine did not reverse CORT group behaviors (2way ANOVA, post hoc Bonferroni $p\leq 0.05$). Corticosterone in drinking water seems to be a reliable anxiety/depression-like state model.

P3-F-144: *Memory modulation by heroin and heroin conditioned stimuli: relevance to addiction*

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Our research group has recently established that injections of opiate agonists, or exposure to their conditioned stimuli (CS), can enhance memory consolidation: a process of memory stabilization that can be influenced by particular experiences. The relevance of these findings to addiction processes, however, has been unclear because drugs are usually self-administered by humans. Therefore, to experimentally tease apart Pavlovian and Instrumental conditioning factors in the memory effects of opiates and their CS, we employed a yoked procedure in Sprague-Dawley male rats. One group was trained to intravenously self-administer (SA) heroin (0.05 mg/kg/inf; FR1) paired with the activation of a light-CS for 12 days (3 h sessions, 1 session/ day). A separate group of yoked rats was individually matched to SA rats receiving an equal number of response non-contingent heroin infusions, as well as heroin CS presentations. SA was followed by 6 days of extinction (Ext) during which responses on the active lever had no consequences. Finally, during the cue-induced reinstatement (R) session, the response-contingent heroin CS was reintroduced in the absence of heroin. The ability of animals to remember the location of objects was tested at different stages of the study within-subjects. For each test, rats were presented with two identical objects in two locations of an open field and immediately tested in self-administration chambers (SA, Ext and R session). After a 72 hr retention period, rats were tested with the same two objects, but one moved to a different location. To our surprise, heroin that was self-administered had no effect on object memory. In contrast, the heroin-paired CS enhanced memory in both groups.

P3-F-145: *Impact of large vessel dilatation in a mice model of Alzheimer's disease*

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Abstract Introduction: Previous post-mortem findings clearly show vascular abnormalities in Alzheimer's disease (AD). While most research has focused on the relationship between small blood vessel leaks and AD, a significant minority of AD patients have large blood vessel dilatation. It is also seen in higher proportions in Hispanic and some Asian populations. The contribution of large blood vessel dilatation to neuroinflammation and AD progression remains poorly understood. Understanding the impact of large vessel changes in AD will allow us to diagnose and specifically target these events earlier in the disease course. Method: To model large blood vessel dilatation, we used the AppNL-F knock-in mouse model of AD and injected elastase in the cisterna magna which causes the major arteries to swell. We assessed the impact of arterial expansion on neuroinflammation, proteostasis, and AD-relevant markers of pathology. Results: With elastase, we found a significant increase (~20%) in basilar artery size compared to vehicle (PBS) injection. Our preliminary results indicate that this dilatation is maintained at least three months post-injection. Using

immunofluorescence, we demonstrate changes in biomarkers of AD (amyloidosis, and tau hyperphosphorylation) following dilatation and evidence of neuroinflammation (astrocytes and microglia). Conclusion: Understanding how large blood vessel dilatation contributes to the progression of AD pathogenesis may help identify potential biomarkers and develop therapies that target this route, as well as preventative strategies to slow disease progression.

P3-F-146: *Place field directionality, position, and size are differentially affected by visual cues*

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The hippocampal indispensability for episodic memories suggests its ability for fast encoding of information of various modalities to create unique episode representation. Hippocampal maps reflect this convergence in place cell properties, which may be independently altered by perturbances in spatial and nonspatial cues. In addition, hippocampal maps demonstrate fast evolution during the first minutes in a new environment. It involves changes in place field location (backward shift), size (expansion), and firing rate (particularly in directional specificity in linear mazes). These changes may reflect fast synaptic modifications underlying episodic memory formation. To understand the mechanisms of fast encoding for different streams, it is crucial to determine which of the fast modifications are controlled by spatial and nonspatial cues. We performed single-unit recordings from hippocampus as rats were exploring a new circular maze for 5 days. The non-spatial cue alterations included temporary unavailability of distant visual cues and a switch of visual context. We found that place field directionality and expansion were minimally affected by the visual cue manipulations. In contrast, the place field backward shift was strongly affected by the availability of visual cues and the context switch. The observed fast modifications of the hippocampal maps diminished with experience in the maze, as was diminished the effect of nonspatial cues on the place field expansion. These findings suggest separate hippocampal mechanisms for fast encoding of spatial and nonspatial information.

P3-F-147: *Age, gender, and task modulation of eye blink behaviour in humans*

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Spontaneous blinking of the eyes is a crucial physiological behaviour. However, it tends to occur at a higher rate than necessary for this purpose alone, suggesting that additional cognitive, social, and

environmental factors may be involved. It has been shown that blinks occur at implicit breakpoints in a task and are sensitive to internal mental states related to attention and cognitive demand. Here, our objective is to characterize eye blink behaviour in healthy controls performing two tasks: a structured interleaved pro- and anti-saccade task and an unstructured video-viewing task. We collected video-based eye tracking data from 608 participants spanning the ages of 5-93 years (390 female, 218 male) on these tasks, and analyzed blink timing and duration. We found differences in blink behaviour between age groups, with blink rate increasing from childhood to adulthood. Female blink rate was higher in those of reproductive age, suggesting a strong hormonal modulation. Additionally, blink behaviour was highly organized within both structured and unstructured tasks, occurring at times with minimal task demands. Participants suppressed eye blinks more often on anti-saccade trials than pro-saccade trials, consistent with stronger inhibitory control on anti-saccade trials. These findings suggest that blink behaviour can contribute to the identification of non-invasive biomarkers related to cognition, memory, and motor ability, which have important implications for early disease diagnosis.

P3-F-148: *Functional Mapping of Cerebellar Neurons During Distinct Behavioral States*

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Cerebellum has been traditionally considered to mostly contribute to motor coordination and motor learning. However, accumulating evidence from human and animal studies has suggested that cerebellum also plays an important role in cognitive processes such as reward, addiction and social behavior. Despite its emerging role in nonmotor function, how the cerebellum integrates the cognitive information from the rest of the brain and more importantly, how it feeds back the processed information to other brain regions remains poorly understood. Here, we systematically mapped the functional connectivity between cerebellar neurons and distinct regions of the cortex by performing wide-field cortical Ca2 imaging and neuropixel recordings in the cerebellum simultaneously. We found that not all cerebellar neurons exhibit stable functional connectivity patterns with the cortex. We showed that the stably cortex-associated cerebellar neurons are diversely affiliated with the cortical networks as the correlation maps show various connectivity patterns; yet these patterns are anatomically defined and consistent with cortical activity motifs, which indicates that the functional connectivity is specific. Furthermore, we found that these diverse connectivity profiles are associated with cerebellar activity of all recorded locations, indicating that the cortico-cerebellar connectivity is not specific to any cerebellar lobule. More interestingly, these connectivity patterns change as the animal goes from anesthetized to awake state, indicating that cerebellar neurons can dynamically integrate information from the cortex depending on the behavioral state. These findings shed light on how cerebellum blend in with cortical networks in cognitive processing.

P3-F-149: *Cortical reactivation of distinct attributes of experience during resting state precedes pattern completion of the corresponding behavioural sequences*

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Pattern Completion is the process by which complete neural representations of experience is elicited upon presentation of partial information. In a recent study (Esteves et al., 2021, Jneuro), we have shown that the pre-motor cortex carries two distinct types of representations: place-cell like activity which relies on an intact hippocampus, and responses tied to visuo-tactile cues which were spared following hippocampal lesion. Taking advantage of these parallel encodings, the present study assessed whether spontaneous cortical retrieval of visuo-tactile attributes of previous experience is followed by completed representations of the spatial trajectories that mice experienced in association with those attributes. We recorded ensembles of neurons in the superficial layers of mouse pre-motor cortex using two-photon Ca2+ imaging, while simultaneously acquiring LFP from the ipsilateral CA1, during periods of quiet wakefulness before and after active exploration over a linear treadmill environment. During the second restful period, we identified two types of reactivation events, which separately conveyed information about spatial trajectories and visuo-tactile cues. Reactivation of cue information preceded that of trajectories in relation to hippocampal SWRs. Furthermore, paired reactivations of cue and trajectory information shared complementary features. In accordance with theories on pattern completion, our results suggest that spontaneous reactivation of cortically encoded attributes may subserve partial patterns used to retrieve spatial information from the hippocampus.

P3-F-150: *Open Field Test: parameter noise in operational definitions*

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Reproducibility is the bogeyman of many life sciences in the 21st century. In the Open Field Test, some of the causes of irreproducibility include mouse strain, test environment, home-cage enrichment, and inter-rater reliability. Here we focus on a less discussed source of potential error: the selection of parameters for behavioural measurements. It is often assumed these parameters, such as the size of the inner-area, are widely agreed upon and robust to small changes. We provide evidence there is noise between scorers and use an automated pipeline to show that small parameter changes are

capable of altering the statistical significance of the results. Our approach is useful for building a big-picture awareness of fluctuations in statistical results that could lead to future problems with reproducibility.

P3-F-151: *Sex differences in the reinforcement enhancing effects of an interoceptive opioid discriminative stimulus.*

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Rationale: Drugs of abuse evoke perceptible changes to the body that influence goal-directed behaviour. Drug discrimination studies can determine how the nature of conditioned associations with such interoceptive stimuli modulate reward-seeking behaviour. In occasion setting, interoceptive effects of the drug function as a feature that disambiguates associations between conditioned stimuli (CSs) and unconditioned stimuli (USs) to activate/inhibit US seeking in response to CS presentations. Such differential learning may influence subsequent drug reinforcement. Method: Male and female rats were given daily intermixed morphine or saline treatment sessions. For feature-positive (FP) assigned rats, on morphine sessions a white-noise CS was followed by access to sucrose (the US); on saline sessions, sucrose was withheld. Feature negative (FN) rats learned the reverse associative contingency. In pseudo-conditioning groups morphine was non-indicative of any CS-US associability. After conditioning, rats self-administered morphine intravenously to assess the impact of training on opioid reinforcement. Results: In males, appetitive (FP) conditioning resulted in enhanced morphine self-administration, resistance to extinction and enhanced reinstatement of self-administration, and enhanced locomotor excitation compared to inhibitory (FN) training. Females did not exhibit such differences. Significance: These results indicate that the nature of a conditioned association with an opioid interoceptive stimulus can alter subsequent opioid reinforcement in a sex-dependent manner.

P3-F-152: *Abrupt pH change does not grossly affect adult zebrafish behaviour*

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In the laboratory, pH may vary in individual holding tanks of frequently employed standalone racks due to differences in stocking density, feeding, and water flow into the tanks. Furthermore, experimental tanks are usually filled with clean water with a pH of 7. Thus, when the fish are placed in such experimental tanks, they may experience abrupt pH change. This change may be stressful to

zebrafish and may be detected as altered behaviour. Here, we conducted a proof-of-concept analysis of the potential behavioural effects of abrupt pH change in zebrafish. We assigned wildtype adults housed in pH 7 water randomly to one of four pH conditions (pH 5, pH 6, pH 7, pH 8). Fish were singly netted into a testing tank with the respective pH value and were monitored for 10 minutes. The swim path of the fish was videorecorded and later analyzed using EthoVision tracking. Unexpectedly, we found no significant effect of pH change on any of the swim path parameters quantified. For example, there were no significant changes in immobility frequency, immobility duration and total distance travelled. Nevertheless, we observed two opposite trends in fish exposed to the two extreme ends of the pH range (pH 5 & pH 8). At pH 5, it suggests a potential increase in intra-individual temporal variance of turn angle while it suggests a potential decrease when exposed to pH 8. These results suggest that an abrupt change in pH, within a range of values expected to occur in the laboratory, does not grossly affect the behavior of zebrafish and may not be stressful.

P3-F-153: *Successful sequential learning despite reduced locomotor activity and depressed neurogenesis in cranially irradiated mice*

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Irradiation studies using >5Gy doses have so far produced conflicting results on hippocampal-dependent behaviours assessed with classical tasks. A critical test for irradiated brain recovery would facilitate detection of short-term and fine effects and essentially address an ability to retrieve and modify previous memories needed to adapt to a constantly changing environment. To this end, we designed a gradually transforming setup allowing us to continuously trace sequential learning, reversal learning, and memory extinguishing in the Intellicage. Mice were first to adapt to the cage drinking corners and restricted water supply (7 days), then find an individually assigned drinking corner (7 days learning followed by 7 days relearning), and lastly drink from randomly changed corners (7 days). Most of the experimental stages were affected by irradiation as detected by ANOVA main effects. 5Gy whole-brain X-ray irradiation decreased animals' locomotor activity (learning, relearning, extinction stages), their correct choices (learning, extinction stages), and also the fraction of mistakes (learning, relearning stages). Despite these and additional effects found on specific days, the irradiated mice effectively learned and relearned the target drinking corners and exhibited unaltered corner preference after memory extinguishing. Notably, the task succession did not potentiate hippocampal neurogenesis inhibited by irradiation. Our data imply a retained ability for

continuous behavioural adaptations and showcases incidental restricted effects explaining previous conflicting results.

P3-F-154: *The role of the dentate gyrus in perceptual discrimination: insights from DG- and CA1-lesion case studies*

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The dentate gyrus (DG) subregion of the hippocampus (HPC) is involved in mnemonic pattern separation, orthogonally representing similar information to allow the formation of separate, fine-resolution memories. This has been demonstrated in BL, a rare individual with 50% cell loss selectively along his DG bilaterally, who shows poor discrimination of highly similar objects in memory. Given that the 'pattern separation' function of the DG is believed to relate to sparse encoding facilitated by DG neurogenesis, we investigated the role of the DG in perceptual (non-mnemonic) discrimination. On an object oddity task, BL's ability to determine the odd object amongst three identical objects was significantly worse than controls. This was accompanied by a pattern of eye fixations suggestive of increased object comparisons. On a series of neuropsychological measures requiring fine-grained perceptual discrimination of abstract designs, line lengths, spacing, sizing, and morphed animals, BL performed in the impaired to low average range compared to normative data. He performed in the low average to average range on easier versions of these tasks. Conversely, BR, an individual with selective CA1 lesions, performed in the average range on all tasks. On neuropsychological verbal and visual learning tasks, BL's encoding over several trials was impaired, but his retention of what he did encode was average. By contrast, BR exhibited average encoding but impaired retention. Collectively, these results indicate the involvement of the DG in perceptual discrimination/encoding and CA1 in memory/retrieval.

P3-F-155: *The smart vivarium: implementation and validation*

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Our capacity to consolidate the behavioral strategies to cope with stress is greatly influenced by social interactions. In a large group, mice are influenced by the stress put by other members of the group over time, resulting in the establishment of a complex social hierarchy. In this dynamic structure, group members interact with each other, play, and fight to consolidate their social rank. The behavioral ability that each mouse exhibits during daily life to control stress determines its status in

the colony. The goal of this project is to develop an automated behavioral platform using machine-learning algorithms and fiducial markers to evaluate and monitor over time the behavioral features exhibited by each member of a complex colony. We have developed a large vivarium equipped with high-quality cameras. We have monitored the behavioral characteristics of mice up to a maximum of 10 mice for 6 weeks in the vivarium and archived the corresponding data. We created an extensive library of several thousand mouse images to automatically detect individuals and identify group behavioral characteristics by tracking them through a hybrid machine system consisting of DeepLabCut with a new MiceTag algorithm. We segmented behavioral sub-categories such as positive, negative, and neutral interactions and validated the accuracy of this classification through manual codification. Overall, our results suggest that our automatic detection and behavioral categorisation algorithm can identify and track every single mouse in a complex colony efficiently over prolonged periods of time. Our findings also support the use of machine-based approaches for an unbiased categorization of mouse behaviors over time. Finally, our vivariu

P3-F-156: *Temporal dynamics in the neocortex do not depend on an intact hippocampus*

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Recent long-term calcium imaging studies have demonstrated that hippocampal and cortical memory representations dynamically change with recurrent exposures to an environment. Considering the critical role of the hippocampus in spatiotemporal memory encoding, the periodic reorganization of hippocampal memory representations may reflect - or be actively driving - the temporal distinction of events. By extension, ongoing hippocampal modulation of context-dependent memory representations may also underlie temporal drift in the cortex. To examine the influence of the hippocampus on cortical dynamics over multiple days, in vivo two-photon microscopy of genetically-encoded calcium indicator mice was used to longitudinally image neurons in CA1, as well as retrosplenial and motor cortices before and after bilateral hippocampal lesions. One cohort of mice was imaged in both familiar and entirely novel environments, and another was tested in a familiar global context where only select local cues were unstable. Consistent with previous studies, both hippocampal and cortical representations exhibited turnover of active spatially-selective cells across experimental days. However, this temporal drift was not dependent on an intact hippocampus in familiar nor novel environments and, rather, decreased in response to changing object-place associations. These results support that single-cell temporal dynamics are an intrinsic feature of both the archicortex and the greater neocortex and representations of learned environments are locally modulated by ongoing experience.

P3-F-157: *Subregion specific processing of Pavlovian reward cues in the nucleus accumbens*

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The neural circuits that guide motivated behavior converge in the nucleus accumbens, which translates salient environmental stimuli into action. The nucleus accumbens is a heterogeneous brain region made up of multiple anatomically and functionally distinct subregions, which receive and process inputs from many parts of the brain onto multiple cell types. How these circuits are organized and how information about reward is relayed through these circuits to drive motivated behaviour is still not well understood. Here we use a head-fixed Pavlovian reward conditioning task and multi-site in vivo fibre photometry to examine how reward-predicting cues are encoded by subregion specific circuits within the nucleus accumbens. We observe distinct patters of activity in the nucleus accumbens medial and lateral shell across the learning and expression of Pavlovian reward conditioning. Our results suggest that cues that drive motivated behaviour are differentially routed to networks of cells in distinct locations within the nucleus accumbens.

P3-F-158: *Cell adhesion molecule 2 deletion reduces impulsivity and voluntary cannabinoid intake, and impairs physiological response to THC in mice*

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It is estimated that 3.9% of the global population uses cannabis annually and that those who use cannabis within their lifetime are at high risk to develop cannabis use disorder. Polymorphisms in Cell Adhesion Molecule 2 (CADM2) were recently implicated in the risk for cannabis use initiation, though this association is correlational. In the present study, we used a Cadm2 knockout (KO) mouse line to investigate the causal relationship of Cadm2 with voluntary cannabinoid intake, THC response, and cognitive phenotypes associated with substance use. During a two-choice edible preference test comparing drug and vehicle cookie dough consumption, KO mice showed lower consumption of and preference for THC- and cannabis oil-containing cookie dough compared to wildtype (WT) and heterozygous (HT) mice. Preliminary results also suggest that acute and repeated injection of THC (3 and 10mg/kg) in KO mice induces hyperlocomotion, and that the hypothermic effects of acute, high-dose THC seen in WT mice are not observed in KO littermates. Finally, using the 5-choice serial reaction time task, we identified multiple genotype-dependent differences in executive functions in drug-naïve mice. KO mice acquired the task faster, committed fewer impulsive errors, and showed impaired attentional performance compared to their WT and HT littermates. Together, these data implicate

Cadm2 in the presentation of impulsive behaviour, physiological response to THC, and the rewarding potential of cannabinoid-containing edibles. These findings provide support for human correlational studies that propose CADM2 polymorphisms affect externalizing phenotypes, including drug initiation and regular use.

3G. Novel Methods and Technology Development

P3-G-159: *A strategy to assess the effect of microgravity on the neuronal cytoskeleton and intracellular trafficking*

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Microgravity exposure plays a role in onset of physiological dysfunction among crew onboard the International Space Station (ISS). Cognitive effects such as loss of motor control and mood impairment are difficult for astronauts, as they impair quality of life and are risk factors for neurological conditions. However, it remains difficult to investigate the underlying cause of such conditions via cellular and sub-cellular experimentation in actual microgravity. Here, in collaboration with HNu Photonics (Maui, HI), we report a framework for use of the imaging and microfluidics platform "Mobile SpaceLab" (MoSL) for cell biology research in actual microgravity. We plan to send cultured SH-SY5Y neuroblastoma cells housed in the MoSL to the ISS (SpaceX27, Jan. 2023) and will investigate the effect of microgravity on 1) neurite outgrowth and microtubule dynamics and 2) axonal transport of fluorescently-tagged mitochondria. Using the MoSL's imaging capabilities, we will collect the first data representing dynamic neurite outgrowth and axonal transport in actual microgravity. Post-flight, we will further analyze these cells for markers of cellular and mitochondrial stress. The results of these experiments may aid in uncovering mechanistic pathways involving microtubule disruption and help explain the maladaptive response to microgravity in neurons, such as decreased neuronal plasticity. Furthermore, success in this mission may open the hatch for follow-up experiments using this framework and MoSL across cell biological disciplines.

P3-G-160: *A template matching algorithm for automatic classification of task-state functional brain networks*

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Functional MRI data obtained during task performance can be analyzed using Constrained Principal Component Analysis, as implemented in the fMRI-CPCA software, to extract task-state brain networks. Typically, components extracted using fMRI-CPCA are analyzed by an expert who uses the anatomical locations of brain activity and the corresponding HDRs to identify the network(s) present. This process is tedious and limits the speed at which networks can be identified, discovered, and validated. Computer vision offers methods for automating the classification of image-based data. Template matching is one such method, where an image to be classified is correlated with one or more sample images (templates) to determine the presence or absence of the template in the image. This work presents a template matching algorithm (UBC Invention ID 2021-092) for the automatic classification of extracted components into one of twelve previously discovered task-state exemplar networks (DOI 10.5281/zenodo.4274397). For each network, a set of 20-30 brain slices that present unique, replicable activation patterns have been identified and are used as the templates. The component is classified based on which network(s) present with the highest total correlation(s) across their respective templates. This algorithm enables detection of multiple networks in a single component and indicates the presence of new networks when the component does not match closely with any of the existing exemplar networks (Z-score < 0.8); this led to the identification of the 12th network in the atlas.

P3-G-161: *A novel mouse model to study endogenous expression, localization, and targets of SUMOylation in the central nervous system.*

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SUMOylation is an essential and evolutionarily conserved mechanism critical for central nervous system (CNS) development and brain function in mammals. This process occurs when Small Ubiquitin Like Modifiers, or SUMO proteins, are covalently bound to protein substrates in a highly dynamic and reversible manner enabling tight spatiotemporal regulation over a wide variety of protein functions. Of the three SUMO paralogs (SUMO1 - SUMO3) shared between humans and mice, Sumo1 and Sumo2 share around 50% homology, whereas mature Sumo2 and Sumo3 are nearly identical. Despite this overlap, researchers are only beginning to understand some of the shared and unique roles for the conjugation of each SUMO-type. Studying SUMOylation in vivo remains challenging as limited tools are available to study SUMO proteins and their targets in their native context. We generated a novel mouse model to study SUMOylation in the CNS by knocking in a hemagglutinin (HA) tag into the endogenous Sumo2 locus. Using this mouse line, as well as a previously established HA-Sumo1 knock-in mouse line, we compare cells enriched for either Sumo1 or Sumo2 in the mouse CNS. Moreover, we performed immunoprecipitation coupled with mass spectrometry to identify existing and novel interactors both unique and shared between Sumo1 and Sumo2 in the mouse brain. This model will serve as a valuable tool to study the cellular and biochemical roles of SUMOylation in the CNS. Future

studies will use this model to uncover context specific substrates and how they regulate neurobiological processes.

P3-G-162: *TRACR: anterograde monosynaptic transsynaptic tracing in mouse*

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Probing the organisation and function of neuronal circuits is essential to the understanding of physiology and pathology. Existing tools are limited by inflexibility, toxicity, or an inability to trace local circuits. We have adapted an established synthetic biology platform to allow for genetically-encoded anterograde transsynaptic tracing in mice. Our system, TRACR (TRanssynaptic Anterograde Circuit Readout), is designed for separate genetic access to the presynaptic and post-synaptic halves of the circuit allowing deep, higher-throughput interrogation of the relationship between synaptically connected neurons. Here, using several approaches, we demonstrate that TRACR can reliably identify known neural circuits in mouse. In long-range circuits, TRACR beginning in excitatory retinal ganglion cells reveals known post-synaptic partners in the dorsal lateral geniculate nucleus (LGN). Within the retina, many neurons respond to motion in only one direction, driven by input from local starburst amacrine cells (SACs). With TRACR starting in SACs, almost all identified post-synaptic cells expressed molecular markers of direction-selective neurons. Functional assessment of post-synaptic cells also showed direction-selective responses. In contrast, beginning TRACR in a broad set of amacrine cells labels an equally broad set of post-synaptic partners with no enrichment for direction-selective neurons. Taken together, this demonstrates that TRACR can faithfully identify post-synaptic partners locally and at a distance. Future directions include: (1) identifying circuits of newly-discovered cell types, (2) identifying the changes in retinal circuits in models of degenerative disease, and (3) screening for factors promoting synapse formation by transplanted cells in retina.

P3-G-163: *Multiscale resolution of mouse brain networks using combined mesoscale cortical Imaging and subcortical fiber photometry*

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Cortical processing of sensorimotor signals underlies many conscious behaviors in mammals. Mesoscale imaging of cortical activity using a cranial window and genetically encoded optical sensors provides a method of studying the interaction between cortical areas in behaving animals. This study

aimed to develop an optical and surgical preparation that preserves wide-field imaging of the cortical surface while also permitting access to subcortical networks. This was achieved by using an optical fiber implanted along with a bilateral widefield window, enabling simultaneous mesoscale cortical imaging, and subcortical fiber photometry recording of calcium signals in a transgenic animal expressing GCaMP. Subcortical signals can be collected from regions including the dorsal striatum, hippocampus, and thalamus. We also combined this approach with multiple sensory-motor tasks, including auditory and visual stimulation, and video monitoring of animal movements and pupillometry in a head-fixed apparatus. We found a high correlation of brain activity, sensory stimuli, and movements. Furthermore, spontaneous recordings revealed that specific motifs of cortical activity are differentially correlated with presynaptic activity recorded in the striatum. This preparation can be used for the dual-color recording of most available green and red genetically-encoded sensors at cortical and subcortical levels with no significant crosstalk. We believe that this method can be utilized to find not only global patterns but also cell-specific connectivities that provide insight into corticobasal circuit organization. Funded by Canadian Institutes of Health Research Fdn-143209 to THM and Fdn-143210 to LAR.

P3-G-164: *Linear-nonlinear model permits inference of synaptic subtype from short term dynamics*

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The effective strength of synaptic connections is known to change on a millisecond timescale which has important implications for the processing of neural information. However, not all synaptic pairings exhibit the same dynamics and understanding the dynamics characteristic of different cell-type pairings is highly important for understanding neural coding. This work compares methodologies for inferring both known cell types and unknown subgroups from short time-scale synaptic dynamics. Both traditional measures of short-term dynamics and the parameters of a recently published linear-nonlinear synapse model were used to represent the dynamics of cell pairings from the Allen Institute Synaptic Physiology dataset. Only the model representation supports accuracy significantly better than a baseline measure when representations are used with standard machine learning techniques to infer known identities in pairs with excitatory pre-synaptic cells. Further, this performance is only significant at a calcium concentration close to physiological levels and is abolished at higher calcium levels further from physiological levels. This reinforces the notion that near-physiological calcium concentration is an important consideration for experimental work interested in capturing nuanced dynamics at this timescale. Several measures also suggest that automatic inference of groupings may be more robust when unsupervised machine learning is based on the model parameter representation. These results support clear ways to capture synaptic dynamics mathematically and

constrain experimental conditions to significantly improve inference of meaningful distinctions in short term synaptic dynamics between cell-type pairings.

P3-G-165: *Whole-brain connectome-based computational modelling of concurrent resting state electrophysiological and hemodynamic activity*

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Whole-brain connectome-based neural mass models are a powerful tool for understanding the activity of the brain measured by neuroimaging technologies such as fMRI, EEG, fNIRS, and other modalities. These models have historically focused on one modality type, and its associated spatial and temporal resolutions, at a time. However, given that concurrent multi-modal datasets are becoming more common and given that the different neuroimaging technologies are measuring the same underlying organ, there is a need for a new generation of connectome-based modelling that accurately simulates brain signals across multiple modalities. Here we demonstrate a new whole-brain modelling framework that allows for concurrent simulation and parameter estimation of electrophysiological and hemodynamic signals. Furthermore, our approach can be used for model fitting and parameter estimation in single-subject datasets. This framework addresses the computational complexity of dealing with vastly different time scales and balances the training error between different modalities. In addition to further constraining the parameter search to more biologically relevant regimes, it opens new possibilities for studying the mechanistic underpinnings of known inter-modal phenomena. We discuss applications of this approach for testing hypotheses regarding the commonly observed anti-correlation between electrophysiological alpha power and hemodynamic signals.

P3-G-166: *Intervention design and pilot study to evaluate virtual reality exposure therapy on people with epilepsy and related anxiety disorders*

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Over 28% of people with epilepsy (PwE) struggle from at least one anxiety disorder, making anxiety the most common psychiatric comorbidity in this population. Exposure therapy (ET) can be helpful in managing anxiety in PwE. Virtual Reality (VR) has been shown to be an effective tool for delivering ET for numerous anxiety disorders. The use of untethered-VR headsets to deliver ET in this population

offers several potential benefits, but to our knowledge no research has been conducted to-date on VR-ET in PwE. We are designing and rigorously evaluating a VR-ET program administered in private residences that focuses on decreasing anxiety in PwE. Our pilot study consists of three phases: 1) Engagement with those with lived-experience related to epilepsy (target n=15) via online surveys to identify and validate three scenarios that each create anxiety at three different levels of severity in PwE. 2) Film nine 360-degree VR-videos (3 scenarios x 3 levels each based on data consolidated from Phase 1 and literature reviews) to offer in the therapeutic intervention. 3) Run a pilot clinical trial that will be registered on clinicaltrials.gov. This prospective experimental study will evaluate the impact of the VR-ET on PwE (target n=10) using mixed-methods. We will measure self-reported anxiety (GAD-7; HADS-A; brEASI; diagnostic protocol proposed by Hingray et al. (2019)) over two weeks as participants transition through the scenario severity levels. We hypothesize that levels of epilepsy-related anxiety will decrease after using VR-ET. Preliminary results will be available by April 2022. This study will contribute to the limited body of research that exists on managing anxiety in PwE. Findings from our pilot will inform the methods for a subsequent larger clinical trial.

P3-G-167: *Building a framework for studying neuro-vascular networks*

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Functional connectivity and graph-theoretical properties of resting-state networks are showing promise as eventual clinical markers of neurological diseases. However, being measured with blood oxygen level-dependent functional magnetic resonance imaging, they reflect the interplay between neurons and blood vessels, which are themselves affected by these diseases. In animal models, direct measures of neuronal and vascular structure and function can be achieved using multiphoton microscopy, but are limited by a trade-off between temporal resolution, spatial resolution, and field-of-view. This poster presents our latest developments towards establishing new tools for studying neuro-vascular interactions across spatial scales in the mouse brain. On the experimental side, we are designing a multimodal microscope combining Bessel focus two-photon microscopy and optical coherence tomography that will allow to record microscale video-rate neuronal and vascular dynamics in 3D volumes in vivo. Mesoscale cortical neurovascular interactions are measured using widefield imaging of fluorescent, intrinsic and speckle contrast signals. On the data science side, we are developing models for integrating vascular parameters into dynamical systems and network models. We hope to stimulate new ideas on the bridging of two neuroscience paradigms, that of neuro-vascular coupling and that of network neuroscience.

P3-G-168: *PyRodentTracks: flexible computer vision and RFID based system for multiple rodent tracking and behavioral assessment*

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PyRodentTracks (PRT) is a scalable and customizable computer vision and RFID-based system for multiple rodent tracking and behavior assessment that can be set up within minutes in any user-defined arena at minimal cost. PRT is composed of the online Raspberry Pi-based video and RFID acquisition and the subsequent offline analysis tools. The system is capable of tracking up to 6 mice in experiments ranging from minutes to days. PRT maintained a minimum of 88% detections tracked with an overall accuracy >85% when compared to manual validation of videos containing 1-4 mice in a modified home-cage. As expected, chronic recording in home-cage revealed diurnal activity patterns. Moreover, it was observed that novel non-cagemate mice pairs exhibit more similarity in travel trajectory patterns over a 10-minute period in the openfield than cagemates. Therefore, shared features within travel trajectories between animals may be a measure of sociability that has not been previously reported. Moreover, PRT can interface with open-source packages such as Deeplabcut and Traja for pose estimation and travel trajectory analysis, respectively. In combination with Traja, PRT resolved motor deficits exhibited in stroke animals. Moreover, PRT can work with conjunction with a two-bottle task setup we developed to simultaneously measure the preference of mice between any two liquids. Overall, we present an affordable, open-sourced, and customizable/scalable rodent-specific behavior recording and analysis system.

P3-G-169: *The heterogeneity of astrocytes in stroke: spatially resolved gene expression reveals the dynamics of astrocytes over time and their interactions with neighboring cells*

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Stroke recovery is a dynamic process that evolves over time. Here, we investigated the processes that mediate recovery from cortical stroke at different time points post-injury in a mouse model of endothelin-1 stroke. We utilized three sequencing strategies: Visium Spatial Transcriptomics, 10X Chromium and a new platform, DISCO (Digital microfluidic Single Cell -Omic), to gain temporally and spatially defined RNA sequencing datasets. Visium was performed on acute (d2), subacute (d10), and chronic (d21) post-stroke brains. With this data we saw an astrocyte-dominant signature at day 10 post-stroke. To further investigate potential roles of astrocytes during the subacute phase, we performed single cell RNA-sequencing using 10X Chromium on GLAST+ cells isolated from the d14

stroke-injured cortex. Finally, with DISCO, we isolated individual astrocytes within and outside the penumbra to identify, validate and discover cell markers and roles of astrocytes governing repair at the injury site. Our datasets compare and highlight the strength of each sequencing platform and the compatibility of each approach. Altogether, a unique combination of sequencing approaches led to a novel, highly resolved, chronicle of the molecular signatures underlying cortical ischemic stroke.

P3-G-170: *A toolbox for the subcellular control of cAMP & cGMP in vivo*

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While recent optogenetic technologies have been demonstrated for the light-dependent regulation of target molecules at the cellular level, their applications to study subcellular processes in the brain of freely-behaving animals remain limited. cAMP and cGMP are ubiquitous second messengers for intracellular signaling pathways, mediating signal transduction and neuromodulation. However, their postsynaptic functions remain elusive in the living brain due to limitations of spatiotemporal specificity of current approaches to acutely perturb their function in target postsynaptic domains. Here, we introduce genetically-encoded subcellular-localized, light-sensitive and constitutively active cAMP and cGMP metabolic enzymes for the non-invasive manipulation of cAMP and cGMP dynamics in target subcellular domains including postsynaptic dendritic spines and dendritic shafts. These subcellular-localized enzymes demonstrate similar enzymatic activity as their soluble counterparts from biochemical assays in vitro. Following biolistic expression in organotypic cultured slices, we observed their subcellular distributions in living hippocampal CA1 pyramidal neurons by two-photon fluorescence microscopy. Furthermore, we virally expressed these subcellular-localized enzymes into target subcellular domains in CA1 pyramidal neurons of the mouse brain. This toolbox for subcellular cAMP/cGMP manipulation is optimized for in vivo studies, to investigate their molecular functions from the level of the synapse to neural network activity in the brain.

P3-G-171: *Cross-Lab and Cross-Species Intracellular Electrophysiology Dataset alignment with Optimal Transport-Based Domain Adaptation*

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The advent of open datasets cataloguing diverse cell types in the mammalian brain offers unique opportunities for further discoveries. However, intracellular electrophysiology datasets can be skewed by technical variables and species-dependent differences. Here, we propose optimal transport-based

domain adaptation (OTDA) for transforming and aligning datasets across labs & species. We then suggest using aligned datasets to allow grouping of similar cell types and subsequently comparing homologous cell types across species. Electrophysiological features were extracted from several open datasets of cortical patch-clamp electrophysiology. First, we aimed to demonstrate the technique's robustness in aligning data. Using mouse data from a single source, a random sample of the data was skewed stochastically. Then, using OTDA, the skewed data was shifted back onto the remaining dataset. The OTDA method showed better original data reconstruction than z-score or min-max normalization. Next, we demonstrated the usefulness of OTDA in understanding similar cell types across datasets. Data from several species (mouse, human, non-human primate) & labs were aligned using OTDA. Visual inspection confirmed the robust alignment of similar cell types. Finally, we performed unsupervised clustering on the aligned data and inspected within-cluster differences between species. Overall, OTDA shows a robust methodology for cross-species and lab comparison of electrophysiological data while acknowledging the intrinsic differences.

P3-G-172: *cognitive state processing for patients with Parkinson's diseases*

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Human cognition is expressed as complex dynamical interactions between distributed brain areas operating in large-scale networks. Parkinson's disease (PD), as the leader among the fastest-growing neurological disorders, directly impact the cognition abilities of patients including resting tremor, muscle rigidity, bradykinesia, impaired posture, and speech/writing issues. Neuromodulation offers optimal ways to reduce symptoms of this disorder by perturbing (modulating) the activity of neurons in a specific region of the brain. To efficiently interfere with the brain and restore brain function, we need to identify the dynamics underlying neurological disorders and adjust neuromodulation parameters when symptoms are predicted to appear. However, the dynamics underlying neurological disorders cannot be easily extracted from high-dimensional recordings of neural activities and associated symptoms. Mathematical modeling and inference methods should be developed to infer representative biomarkers underlying neurological disorders. In this research, we propose a computational framework to infer a cognitive state, a low dimensional representation underlying the interactions between high-dimensional neural activities and behavioral signals, which can be used as a control signal in neuromodulation system to perturb the brain's circuit's activity with purpose of changing state of the disease or cognition. Specifically, we propose a computational model, called the heterogeneous input discriminative-generative decoder (HI-DGD) that is able to decode a cognitive state from both neural and behavioral signals simultaneously. Then we investigate how a neuromodulation system can use this inferred cognitive state to perturb the brain circuit's activity with purpose of changing state of cog

P3-G-173: *Influence of neural heterogeneity on the response of excitatory and inhibitory networks to periodic brain stimulation in a leaky integrate-and-fire model*

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Low frequency neural oscillations have been detected under various subject conditions and have been associated with a wide array of brain functions, including attention and memory. Since we do not have the experimental techniques to disambiguate the contribution of individual neurons from network activity, many questions remain surrounding the brain's harmonics and their biomedical implications. We propose a computational model that reproduces biophysical spiking behaviour under oscillatory stimulation to better understand the response of a heterogenous network to periodic drives. Using the leaky integrate-and-fire method, we build a heterogenous network model of excitatory and inhibitory neurons. The network was set in an asynchronous regime, incorporated neuron specific excitability, and its response to various stimulation parameters was investigated. We investigated how increasing neuron specific heterogeneity impacted the response of excitatory and inhibitory populations; we explored how changes to the periodic stimulation balanced neuron-neuron interactions and impacted the system's ability to form activity assemblies/groupings. These explorations may reveal methods to provoke or deter groupings in heterogenous populations, providing a deeper understanding of how to manipulate or control network behaviour in a biomedical setting.