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16th Canadian Neuroscience Meeting Abstract Proceedings

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PRESIDENTS WELCOME

Dear Colleagues and Friends,

Bienvenue/welcome to the **16th Annual Canadian Neuroscience Meeting** in Montréal, Québec. We are thrilled to have your participation at this year's meeting. The annual meeting has become a cornerstone for gathering of the neuroscience community in Canada and an outstanding opportunity for networking, sharing our science, and getting together with old and new friends.

The Meeting Chair, **Ian Winship**, and Co-Chair, **Stephanie Fulton**, have assembled a wonderful Scientific Program, featuring talks by neuroscience leaders from Canada and abroad. **Natasha Rajah**, Chair of the Local Organizing Committee, has also done excellent work in organizing the public lectures on ***Diet, Obesity and the Brain*** and the social events at the meeting. **Karun Singh** and **Liisa Galea**, Chair and Co-Chair of the CAN Advocacy Committee, have assembled an exciting advocacy lunch discussing how to build capacity in neuroscience research through Canadian Moonshot programs. Last but not least, **Jibran Khokhar** and the CAN Equity, Diversity, and Inclusion Committee have organized an important panel discussion on ***Life and Neuroscience*** featuring our Presidential, Keynote, and Plenary speakers. Diverse Plenary and Parallel Symposia proposed by CAN members complete the presentations of the scientific program.

We are very pleased to have **Flora Vaccarino** (Yale School of Medicine) deliver the CAN Presidential Lecture on modeling human brain development, **Sheena Josselyn** (SickKids) present the Keynote Lecture on mechanisms of memory formation, and **Ole Kiehn** (University of Copenhagen and winner of the 2022 Brain Prize) present on groundbreaking work on neural circuits controlling movement. We also have an exciting series of Plenary Lectures presented by outstanding scientists including **Dana Small** (McGill University/Yale School of Medicine), **Maja Jagodic** (Karolinska Institutet), and **Hugo Bellen** (Baylor College of Medicine). CAN is also pleased to honor **Karim Nader** (McGill University) for pioneering discoveries on memory reconsolidation.

A special highlight of our meeting will be the lectures by award-winning young neuroscientists. We are pleased to host our two CAN 2023 New Investigator Award winners **Arkady Khoutorsky** (McGill University) and **Bratislav Misic** (McGill University). We are also privileged to have presentations by the top three winners of the CAN-CIHR-INMHA Brain Star Award, **Shannon Tansley**, **Sébastien Tremblay**, and **Lauren Seabrook**.

Among the most engaging sessions are always the poster sessions, featuring the important work of trainees across the country and abroad. We look forward to meeting and discussing exciting results with poster presenters in these sessions.

Remember to visit our sponsor and exhibitor booths to learn about how these organizations play a vital role in enabling neuroscience research across the country. Our sponsors and vendors help make this meeting possible.

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We look forward to welcoming you in Montréal and hope that you have a wonderful experience at this year's meeting!

Keith Murai, President of the Canadian Association for Neuroscience

KEYNOTE AND PLENARY TALKS

PRESIDENTIAL LECTURE

Modeling human brain development with stem cells and organoids: past, present, and future
Flora Vaccarino | Yale University

Since the discovery of induced pluripotent stem cell (iPSC) a decade ago, iPSCs and brain organoids have become a widely used tool to investigate human brain development, from early patterning of neuroepithelial cells into broad regions to the emergence of neuronal and glial cell lineages and their interconnections to form functional networks. Cellular diversity is largely driven by the activity of regulatory elements, primarily enhancers, and their cognate transcription factors that undergo dynamic changes during differentiation, activating or repressing cell fate genes in a species- specific and time-dependent manner. Brain organoids reveal with unprecedented details how cellular diversity emerges in the brain, the variation in human neurogenesis across multiple genetic backgrounds, and how differentiation trajectories are impacted by neuropsychiatric disorders. Brain organoids from individuals with developmental disorders such as autism and Tourette syndrome reveal imbalances in excitatory and inhibitory neurogenesis. Such imbalances could be explained by altered regulatory relationships between transcription factors, enhancers and target genes driving the generation of excitatory and inhibitory neurons in the forebrain. While organoids can survive for months in vitro and yield more mature neurons and glial cells, the lack of a vascular structure and immune cells limit their use for modeling adult-onset diseases. Nevertheless, organoids shed light onto individual trajectories of early neurodevelopment and reveal intrinsically different disease subtypes that could be used as potential stratifying factors in clinical or genetic studies.

FEATURED PLENARY SPEAKER 1

The wisdom of the body
Dana Small | Yale University

Optimal decision making in a changing environment requires evidence accumulation. Typically, this evidence is amassed from the external environment. Within this framework unconditioned rewards are encapsulated within the outcome of an action, for example, the consumption of the food and the oral sensation simultaneously evoked. Here it will be argued that evidence must also be accumulated from the internal milieu and a revised view of food reinforcement learning will be presented that is based upon the integration of external and internal sources of evidence accumulation. Specifically, emerging work from our and other laboratories demonstrates that the critical signals underlying food reinforcement are generated during nutrient metabolism and are conveyed outside of conscious awareness to the brain to modulate dopamine release and support learning. According to this view, conscious oral sensations serve as both outcomes (e.g., the red strawberry is sweet as expected) and predictions (e.g., X amount of sweetness predicts X amount of glucose), enabling the formal integration of conscious and unconscious nutrient sensing so that the value of environmental stimuli are updated based on their nutritional associations. These gut-brain circuits include multiple reinforcing pathways that enable interactions between macronutrients to potentiate reinforcement and promote intake

variety. They are also flexible and adapt overtime time to tune perception, metabolism and learning to a changing food environment to optimize behavior according to the wisdom of the body.

BRAIN PRIZE LECTURE

Brainstem circuits for locomotion in the healthy and diseased brain

Ole Kiehn | University of Copenhagen

Locomotion is a universal motor behaviour that is expressed as the output of many integrated brain functions. Locomotion is organised at several levels of the nervous system, with brainstem circuits acting as the gate between brain areas regulating innate, emotional, or motivational locomotion and executing spinal motor circuits. To be executed, locomotion requires dynamic initiation and termination and appropriate directionally.

This lecture will focus on recent advances that have elucidated the functional organisation of brainstem motor circuits in mammals needed to perform these roles. It will show that designated command pathways in the brainstem control the episodic expression of locomotion and that directionality of locomotion is controlled by activity in discrete brainstem circuits. The lecture will also show how these brainstem circuits are linked to higher brain centres and how locomotor disturbances following e.g. basal ganglia disorders may affect these circuits and how targeted manipulation of brainstem command pathways may alleviate motor disorders.

FEATURED PLENARY SPEAKER 2

Deciphering mechanisms of Multiple Sclerosis development and progression

Maja Jagodic | Karolinska Institutet

Multiple Sclerosis (MS) is a leading cause of unpredictable progressive disability in young adults. The disease is characterized by the autoimmune destruction of myelin and subsequent neuronal loss. Although the exact cause remains unknown, vast epidemiological data establish MS as a complex disease influenced by genetic and environmental factors. Epigenetic mechanisms, such as DNA methylation, orchestrate activity of the genome in response to environmental cues and may provide understanding of molecular mechanisms underpinning disease development and progression. One of the main challenges with studying diseases such as MS is the limited access to the target tissue - the brain. Advances in methods to survey epigenetic modifications genome-wide and from them infer genome activity and cellular states, opened up possibilities to study brain tissue and mechanisms that underlie neurodegeneration.

To understand MS pathogenesis, we are profiling epigenetic patterns in diverse biosamples from data-rich clinical cohorts in combination with functional studies using in vitro and in vivo experimental models. Our data suggest a role of epigenetic alterations of immune cells in mediating the effect of genetic and environmental triggers and implicate changes in neurons and glia in progressive disease. Moreover, we explore possibilities for identifying factors affecting disease progression using easily accessible tissues and epigenetic signatures shared between brain and blood. Our data propose that

epigenetics might shed light on clinically relevant and modifiable mechanisms acting throughout the trajectory of MS.

KEYNOTE LECTURE

Making memories in mice

Sheena Josselyn | SickKids

Understanding how the brain uses information is a fundamental goal of neuroscience. Several human disorders (ranging from autism spectrum disorder to PTSD to Alzheimer's disease) may stem from disrupted information processing. Therefore, this basic knowledge is not only critical for understanding normal brain function, but also vital for the development of new treatment strategies for these disorders. Memory may be defined as the retention over time of internal representations gained through experience, and the capacity to reconstruct these representations at later times. Long-lasting physical brain changes ('engrams') are thought to encode these internal representations. The concept of a physical memory trace likely originated in ancient Greece, although it wasn't until 1904 that Richard Semon first coined the term 'engram'. Despite its long history, finding a specific engram has been challenging, likely because an engram is encoded at multiple levels (epigenetic, synaptic, cell assembly). My lab is interested in understanding how specific neurons are recruited or allocated to an engram, and how neuronal membership in an engram may change over time or with new experience. Here I will describe data in our efforts to understand memories in mice.

FEATURED PLENARY SPEAKER 3

Lipid droplets in Alzheimer's Disease

Hugo Bellen | Baylor College of Medicine (BCM)

Studies in the Bellen lab initially aimed at delineating the role of mitochondrial variants associated with rare neurological diseases, such as Leigh Syndrome and Charcot-Marie-Tooth Disease, have provided insight into the role of mitochondrial function and lipids in these rare diseases as well as in more common neurodegenerative disease, such as Alzheimer Disease (AD). Loss of genes that encode mitochondrial proteins can lead to elevated levels of reactive oxygen species (ROS) in neurons. ROS, in turn, induces the formation of lipids that are peroxidated and subsequently transferred to glia where they are sequestered in lipid droplets (LDs). This process is mediated by apolipoproteins and requires ABCA transporters (Eato and ldd) in neurons, which mediate transfer of lipids to Glial Lazarillo (GLaz), a secreted apolipoprotein. Lipidated GLaz is taken up via receptor-mediated endocytosis (requiring LRP1 and proteins required for endocytosis: PICALM, CD2AP, and AP2A2). Glia then sequester the lipids in LDs, a process which is neuroprotective and limits the oxidative damage due to ROS. Our work indicates that many genes that are required for glial LD formation have been identified as playing a role in AD. Our data also show that the proteins that play a role in LD formation in glia play a role in clearing of Aβ42. Indeed, combining ROS and elevated Aβ42 production strongly exacerbate neurodegeneration and enhance Aβ deposition in flies and mice. Finally, quenching ROS by using N-acetyl-cysteine amide is a potent suppressor of neurodegeneration.

NEW INVESTIGATOR AWARD 1

Peripheral and central mechanisms of chronic pain

Arkady Khoutorsky | McGill University

Chronic pain is one of the leading causes of long-term disability and suffering in humans, affecting ~20% of the population. Chronic pain can be caused by several conditions including nerve injury, inflammation, viral infection, autoimmune diseases, cancer, metabolic disorders, and in some cases appear without any recognizable trigger such as in fibromyalgia. Available treatments have limited efficacy and only 30-40% of chronic pain patients report a satisfactory pain relief. This is the result of an incomplete understanding of chronic pain pathophysiology, leading to the development of therapeutic approaches that target the symptoms of chronic pain and not underlying mechanisms. Following initial insults to the tissue (e.g. nerve injury, inflammation, viral infection, or metabolic disorders such as diabetes), the somatosensory system undergoes a dramatic reorganization, leading to aberrant maladaptive plasticity at peripheral, spinal, and supraspinal levels, and consequently causing sensitization of the somatosensory system and pain. Understanding the fundamental mechanisms of peripheral and central sensitization is a key for developing more efficient and safe therapeutics. Plasticity of neuronal circuits is mediated by modification of existing proteins, for example via phosphorylation events, and by new gene expression. These biochemical changes support the sensitization of the pain pathway via numerous mechanisms, including increased activity of channels and receptors, structural changes, alterations in neuroimmune interactions, and functional rewiring of neuronal circuits. In this talk, I will present studies from my lab focusing on mechanisms underlying peripheral and central sensitization and their roles in animal models of chronic pain.

NEW INVESTIGATOR AWARD 2

Tools for multi-scale, multi-modal annotation of brain networks

Bratislav Misic | McGill University

Imaging technologies are increasingly used to generate high-resolution reference maps of brain structure and function. Modern scientific discovery relies on making comparisons between new maps (e.g. task activations, group structural differences) and these reference maps. Although recent data sharing initiatives have increased the accessibility of such brain maps, data are often shared in disparate coordinate systems (or ``spaces''), precluding systematic and accurate comparisons among them. Here I will describe the main challenges and proposed solutions for a more integrative approach to interpreting brain maps. I will introduce new methods for accessing, transforming, and analyzing structural and functional brain annotations. Our initial efforts have yielded multiple curated reference maps and biological ontologies of the human brain, including maps of gene expression, neurotransmitter receptors, metabolism, neurophysiological oscillations, developmental and evolutionary expansion, functional hierarchy, individual functional variability, and cognitive specialization. We have also implemented multiple methods to generate high-quality transformations between four standard coordinate systems commonly used in neuroimaging research. Finally, we provide robust quantitative assessment of map-to-map similarity via a suite of spatial autocorrelation-preserving null models. Altogether, these methods

combine open-access data with transparent functionality for standardizing and comparing brain maps, providing a systematic workflow for comprehensive structural and functional annotation enrichment analysis of the human brain.

PLENARY SYMPOSIA

Plenary Symposium 01: Gut feelings: Peripheral and central regulation of motivational and affective states by gut signals

How the gut changes behaviour in intestinal inflammation

Keith Sharkey | University of Calgary

Chronic peripheral inflammatory diseases, including inflammatory bowel diseases of the gastrointestinal tract, are associated with many behavioural co-morbidities. These “sickness behaviours” include anxiety, depression, fatigue, social withdrawal, cognitive difficulties and sleep disturbances. Some of these behavioural comorbidities may be associated with pain that also occurs with inflammation, however, this is not the only cause of these conditions. In order to better understand them, we have investigated the mechanisms of anxiety-like behaviours using animal models of intestinal inflammation. Our data show that intestinal inflammation alters the enteric microbiota of the gut and that fecal microbiota transfer from donors with experimental colitis or following recovery from colitis can transfer anxiety-like behaviour and visceral pain, respectively, to otherwise healthy recipients. We also show that leukocyte trafficking to the brain elevates proinflammatory cytokines in the CNS and these contribute to anxiety-like behaviour. Other CNS mechanisms that are important for the development of anxiety-like behaviour are microglial activation, and alterations in endocannabinoid signaling driven by central corticotropin releasing factor type 1 receptor signaling; blocking or reversing these changes reduces anxiety-like behaviour. Increases in excitability of CNS circuits are also a consistent feature of peripheral inflammation and these may underlie the behavioural symptoms that are observed in these models. Taken together, our data show that the gut-brain axis is important in the development of sickness behaviours in intestinal inflammation.

Microbes and mental health: Translating preclinical findings to the clinic

Jane Foster | McMaster University

Researchers in psychiatry and neuroscience are increasingly recognizing the importance of gut-brain communication in mental health. Based on a foundation of animal studies demonstrating the vital role for microbiota-brain communication in brain development, behavior, and brain function over the life span, clinical studies have started to consider the microbiome in psychiatric disorders. Work to date by our group and others suggest that microbiota-immune-brain signaling is an important pathway that infuences brain structure, gene expression of stress-related and plasticity-related genes, stress-reactivity, and behaviour. Ongoing work in our lab is interested in determining the importance of peripheral T cells in the maturation of the microbiome, microbe and host metabolism, and neurodevelopment. The composition, diversity and function of commensal microbes is influenced by genetic, lifestyle, and environmental factors. Our increasing knowledge on pathways and involved mediators along the gut-brain axis has revolutionized our understanding of brain-body interaction. Intestinal bacteria act along the gut-brain axis in part by modifying the immune response. On the other side, bacteria produce neuroactive mediators and can modulate neuronal function, plasticity and behavior. Our recent research has focused on the bidirectional communication between microbiota and T cells in mouse models and in

clinical popupations. This presentation will highlight this work in the context of recent developments linking microbiota to behaviour and brain function. Understanding the influence of microbiota-brain axis on brain function and behaviour is essential to understanding how host-microbe interactions are essential regulators of both physical and mental health. Understanding the basis of these differences, their functional impact, and mapping them to clinical symptoms, severity, and host biology is the next step in this fast-moving area of research. Moveover, the opportunity to harness our knowledge of the microbiome to develop novel therapies and to improve outcomes in psychiatry will be discussed.

Ghrelin-endocannabinoid system interactions in the VTA in the regulation of food reward
Alfonso Abizaid | Carleton University

Ghrelin, a peptide hormone primarily produced by the stomach and upper intestinal tract, binds to receptors in the central nervous system to modulate behaviors associated with increased feeding in response to negative energy balance states including chronic stress. The sites of action for these effects include the ventral tegmental area (VTA), a region that contains dopamine neurons linked to affective behavioral responses including reward seeking behaviors. Within the VTA, about 50-60 of these dopamine neurons express the only known ghrelin receptor, the growth hormone secretagogue receptor (GHSR), and these cells respond to GHSR stimulation by increasing their firing frequency and by releasing dopamine at terminal regions like the nucleus accumbens. Direct ghrelin infusions in the VTA also result in increased food intake and food motivation in rodents. Here we present data showing that the GHSR is present in several cell types within midbrain structures like the VTA and including dopamine producing neurons in mice and rats. Moreover, in some structures the GHJSR is co-expressed with CB-1R in non-dopaminergic cells. We also show that alterations in GHSR signalling result in alterations in cannabinoid signalling within the VTA, and that blocking the cannabinoid receptor-1 subtype (CB-1R) attenuates the effects of ghrelin on food intake and motivation when infused into the VTA. Electrophysiological experiments demonstrate that ghrelin increases dopamine cell excitability in part through an increase in pre-synaptic excitatory tone, and that this increase is prevented by CB-1R antagonists. All of these data together point to a multilayered effect of ghrelin on VTA neurons that promotes excitatory tone on dopamine cells and that is dependent on the release of endocannabinoids to enhance food motivation.

Plenary Symposium 02: Neuroimmune interactions: when the immune system shapes the Central Nervous System

Rhythms of neuroinflammation and chronic pain in EAE: what's time got to do with it?
Nader Ghasemlou | Queen's University

People living with multiple sclerosis (MS) experience disruption to their circadian (24-hour) rhythms and report daily fluctuations in pain and fatigue. An emerging theory is that the neuropathology of MS is linked to circadian rhythm, as people experience circadian disruption are at higher risk for MS. We therefore sought to identify whether pain and neuroinflammation are under circadian control in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. We found that mechanical sensitivity measured by the von Frey assay was increased at ZT8 (where ZT0=lights on and ZT12=lights off) compared to ZT2, 14, and 20, suggesting a circadian rhythm to this pain modality. Flow cytometry of

the lumbar spinal cord revealed altered rhythms in the infiltration/activation of immune cells. Furthermore, some changes in clock gene mRNA rhythms were identified in the ventral spinal cord of EAE mice, where inflammation is strongest. These findings suggest a potential role for circadian disruption in the pathology of EAE. Locomotor activity, a measure of circadian rhythmicity, was assessed. We show that EAE mice do not have disrupted locomotor activity rhythms, indicating that the observed circadian disruption is likely limited to peripheral clocks. This work provides new insights into the role of circadian rhythms in neuroimmune interactions and disease outcomes in EAE, which may also affect those living with multiple sclerosis.

Molecular mechanisms underlying T cell-oligodendrocytes direct interactions
Catherine Larochelle | Université de Montréal

Multiple Sclerosis (MS) is a chronic demyelinating inflammatory disorder of the central nervous system (CNS) affecting 1/500 Canadians. Oligodendrocyte/myelin sheath injury is a key pathological hallmark of MS. The exact mechanisms driving oligodendrocyte injury in MS are poorly understood and no neuroprotective therapeutic strategy is available. Nevertheless, it is well established that the immune system participates to the destruction of myelin and modulates repair mechanisms. Myelin-reactive pro-inflammatory CD4 Th17 cells are pivotal immune mediators in MS and its animal model experimental autoimmune encephalomyelitis (EAE). However, oligodendrocytes are devoid of MHC-II, precluding the classical Th17 cell/target cell interaction. Using two-photon (2P) live imaging in EAE, we have recently shown that activated Th17 cells can form prolonged direct contacts with oligodendrocytes in vivo, regardless of their antigen specificity. Notably, we found that 10-20% of CD4+ T cells observed within the CNS parenchyma of both MS and EAE are in direct juxtaposition to oligodendrocytes. In human and murine oligodendrocytes, using single cell RNA sequencing, flow cytometry and immunofluorescence studies on CNS tissue, we found that a significant proportion of mature oligodendrocytes express cell adhesion molecules in multiple sclerosis, in experimental autoimmune encephalomyelitis and in controls, although their regulation differs between human and mouse. We observed that exposure to pro-inflammatory cytokines or to human activated T cells are associated with a marked downregulation of the expression of melanoma cell adhesion molecule but not of activated leukocyte cell adhesion molecule at the surface of human primary oligodendrocytes. Furthermore, we used in vitro live-imaging, immunofluorescence, and flow cytometry to determine the contribution of these molecules to Th17-polarized cell adhesion and cytotoxicity towards human oligodendrocytes. Our data suggest that ALCAM is a ligand for Th17-polarized cells and contributes to their adhesion to oligodendrocytes and subsequent immune-mediated damage in neuroinflammatory conditions.

Glial interactions regulating myelin health
Veronique Miron | University of Toronto

Myelin is the insulating layer surrounding axons which is required for central nervous system (CNS) health and function. Malformation of, or damage to, myelin therefore contributes to CNS dysfunction in neurological conditions across the lifespan, for which there is an unmet demand for therapeutics targeting myelin health. In this presentation, I will discuss the critical roles of microglia in regulating

myelin across the lifespan in health and disease. In development, we uncovered that although microglia are dispensable for myelin formation, their dysregulation is sufficient to interfere with this process following adverse birth events. During homeostasis, we unexpectedly discovered that microglia are required to prevent the overgrowth and subsequent degeneration of myelin, and associated cognitive impairment. Following myelin damage, we elucidated that remyelination is driven by a dynamic transition in microglia functional states, controlled by microglia turnover. Overall, our work points to the importance of microglia in regulating myelin, and reveals microglia as promising therapeutic targets for the maintenance and restoration of myelin health in disease.

Plenary Symposium 03: Emerging molecular mechanisms of neurodegeneration

Immune signaling in Parkinson's disease: perspectives of a mitochondria
Heidi McBride | McGill University

The loss of dopaminergic neurons in Parkinson's disease has been linked to mitochondrial dysfunction. Evidence for this was initiated in studies showing that mitochondrial complex I inhibitors can initiate disease, and in cell biological studies showing that PINK1 and Parkin mutants may lead to failed clearance of damaged organelles. However, the loss of PINK1 or Parkin in mouse models is not sufficient to cause disease, and most analysis of mitochondrial clearance in vivo shows no change in tissues lacking PINK1 or Parkin. We have shown critical roles for PINK1 and Parkin as repressors of mitochondrial antigen presentation upon infection or heat stress. This process occurs through the generation of mitochondrial derived vesicles triggered during infection and the cargoes within these vesicles can be processed and presented on MHCI molecules to drive the adaptive immune system. Bacterial infection in PINK1 KO mice was seen to induce mitochondrial antigen presentation within antigen presenting cells, resulting in a clonal expansion of mitochondrial specific CD8+ T-cells and ultimately the retraction of dopaminergic neuron terminals within the striatum and PD-related phenotypes 8-12 weeks following infection. These data led to a series of unanswered questions both mechanistically and physiologically to explain the series of events linking the gut infection, alteration in the adaptive immune response, and how these changes resulted in dopaminergic neuron retraction. I will summarize new findings from our collaborative team and focus on the mechanistic links that drive the innate to adaptive immune response. I will present results from genome-wide screens that have identified a series of PD related proteins acting along a common pathway that function within a mitochondria-to-lysosome axis, providing a framework to investigate how cells balance infection induced innate to adaptive immunity with pyroptotic cell death.

Fatty acid desaturation: an unexpected role in the pathophysiology of Alzheimer's disease
Karl Fernandes | Université de Sherbrooke

The brain is considered the body's most lipid-rich organ outside of adipose tissue itself. Lipids constitute over half of the brain's dry weight and are comprised of thousands of molecular species that are used as membrane structural molecules, intra- and inter-cellular signaling metabolites and mitochondrial energy sources. While multiple lines of evidence now implicate disturbances in lipid metabolism (i.e., lipid uptake, synthesis, transport and/or breakdown) during the pathogenesis of Alzheimer's disease (AD),

specific lipid metabolism pathways that are involved and that could be targeted to intervene in AD pathogenesis remain unclear. Here, I will describe work from my laboratory identifying, characterizing, and modulating neutral lipid accumulations in AD and AD mouse models. Lipidomic analysis of AD-associated neutral lipid accumulations highlighted that dysregulation of the balance between saturated and monounsaturated fatty acids (SFA and MUFA, respectively) is an early, pre-symptomatic event during AD progression. Pharmacological targeting of stearoyl-CoA desaturase (SCD), a delta-9 desaturase catalyzing the conversion of SFA to MUFA, restores the SFA/MUFA balance in AD mice and results in a wide spectrum of beneficial effects on neural stem cell activity, microglial activation, dendritic spines and structure, immediate-early gene expression, and hippocampal-dependent learning and memory. Thus, SCD-regulated mechanisms link the genetic triggers of AD to downstream immune, synaptic, and functional impairments. These findings support the concept of targeting lipid metabolism pathways to normalize the SFA/MUFA balance as a novel therapeutic strategy in AD.

Protecting neurons from degeneration by autolysosomal exocytosis
Maria Ioannou | University of Alberta

During oxidative stress neurons release lipids that are internalized by glia and stored in lipid droplets. This process maintains the health of the nervous system. Defects in this coordinated process play an important role in several neurodegenerative diseases, most notably in Alzheimer's disease. Yet, the mechanisms of lipid release and its consequences on neuronal health are unclear. Here, I will discuss our work describing how lipid release by autolysosome exocytosis protects neurons from cell death. During oxidative stress, neuronal lipids become damaged by reactive oxygen species resulting in lipid hydroperoxides. Accumulation of lipid hydroperoxides can induce a biochemically distinct form of cell death, called ferroptosis. Using primary cell culture or fly retina, we discovered that neurons release peroxidated lipids through exocytosis of autolysosomes. We observe lipids within membrane-bound lipid-protein particles by transmission electron microscopy and demonstrate that these particles are released from neurons using cryo-electron microscopy. Failure to release these lipid-protein particles causes lipid hydroperoxide accumulation and cell death by ferroptosis. Our results reveal how neurons use autolysosomal exocytosis to protect themselves from peroxidated lipids generated during oxidative stress. Given the number of brain pathologies that involve ferroptosis, defects in this pathway likely play a key role in the pathophysiology of neurodegenerative disease.

PARALLEL SYMPOSIA

Parallel Symposium 01: White Matter matters: the role of myelin in cognition

PS01.01: Learning to be on time: How white matter plasticity shapes brain dynamics and function

Afroditi Talidou[1], Paul Frankland[2], Donald Mabbott[2], Jeremie Lefebvre[1]
[1]University of Ottawa, [2]The Hospital for Sick Children

BACKGROUND AND AIM: A good half of the volume of the human brain is made of cables. These cables, bundles of axons that we collectively call white matter, connect brain areas and control brain traffic. The conduction properties of these cables (i.e. how fast neural electrical signals go) are influenced by a substance called myelin. Formed by glia, myelin plays a key role in brain function: shown to be essential to memory, compromised white matter integrity leads to the dramatic consequences seen in diseases such as multiple sclerosis and epilepsy. Traditionally thought to be static after development, new results show that white matter rewires itself with experience and learning, complementing synaptic plasticity to support learning. However, activity-dependent myelination impacts brain dynamics and function across spatial (microns to meters) and temporal (milliseconds to years) scales, it is incredibly difficult to study using experiments alone. Luckily, this problem is amenable to computational modeling. METHODS: We investigate activity dependent myelination and its role in maintaining the flexibility and stability of neural circuits function, using a combination of modelling and experimental data, at the level of cortical microcircuits and across white matter. We built and analyzed a variety of neural network models endowed with adaptive, activity-dependent axonal conduction delays, to examine the consequences of such neuron-glia feedback on neural dynamics at various spatial and temporal scales. Specifically, we studied axonal myelination patterns, how they change, and how axonal conduction influence neural activity to support neural communication and synchronization using a combination of modelling and simulations informed by human neuroimaging data. RESULTS: Our modelling results show that ADM implements a gain control mechanism that enhances neural firing rates, correlations and synchrony through the temporal coordination of neural signaling, by normalizing conduction delays along axons of various lengths. This process enhances the resilience of brain dynamics notably by compensating changes in network connectivity that occur through development, learning as well as in presence of injury. CONCLUSIONS: White matter plasticity represents a homeostatic gain and timing control mechanism, where synaptic and axonal/glial plasticity play complementary roles in implementing, preserving and imparting flexibility to brain function.

PS01.02: Myelination in the aging mouse brain

Kendra Furber[1], Stuart Read[2], Scott Rosendahl[2]
[1]University of Northern British Columbia, [2]Canadian Light Source

BACKGOUND: Aging is associated with the degeneration of white matter tracts in the central nervous system (CNS). The structure of white matter tracts over the lifespan suggests a switch from net myelination in early adulthood to net myelin loss in later years. The loss of myelin in cortical white matter has been correlated to cognitive decline, but little is known about the underlying biochemical

alterations that contribute to degeneration METHODS: To characterize age-related myelin degeneration in the mouse brain, electron microscopy and Fourier transform infrared (FTIR) spectroscopic imaging was performed in male C57BL/6 and Sirt2-/- mice over the life span. RESULTS: Aged mice showed an increase in the percentage of unmyelinated axons in the corpus collosum, particularly in mid to large size axons. Chemical imaging via infrared spectroscopy identified alterations in bond vibrations characteristic of phospholipids in this white matter tract including the acyl fatty acid chains, the ester linkage between the glycerol backbone and fatty acid moiety, and the phosphate linkage between the glycerol backbone and polar head group. These biochemical changes in were observed prior to myelin loss and most predominant in the anterior cortical regions. Sirt2-/- mice displayed enhanced myelin degeneration compared to the C57BL/6 background strain. CONCLUSIONS: Several parallels can be drawn between age-related degeneration of white matter tracts in the human and mouse CNS. Chemical imaging allows for the label-free assessment of biomolecules in situ providing insight into the molecular underpinnings of white matter degeneration. A better understanding of the biochemical alterations leading to the loss of myelin is key to developing strategies to promote healthy brain aging.

PS01.03: Remyelinating potentials of stigmasterol in vanadium-induced neurotoxicity and cognitive impairments

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BACKGROUND AND AIM: Vanadium is a strong occupational and environmentally toxic metal that has been recognized to be acutely toxic by most routes of introduction following exposure in large doses. Vanadium compounds are released into the environment at high levels by the steel and mining industries as well as by the fossil fuel industry. Exposure to vanadium in its different forms accumulates in the brain causing central nervous system depression, tremors, behavioral deficits, neurasthenia, severe cognitive and motor deficits. Its neurotoxicity has been closely linked to the induction of oxidative stress that leads to reactive oxygen species generation, lipid peroxidation, neuroinflammation, and neurodegeneration. In a bid to ameliorate the toxicity due to exposure to this metal, we pioneered the isolation of stigmasterol (a known phytosterol) from Grewia carpinifolia. We investigated its abilities in promoting myelinogenesis and enhancing cognition following neurotoxicity induced by vanadium. METHODS: Using in-vitro antioxidant assays [1-Diphenyl-2-picryl hydroxyl (DPPH) quenching assay, ferric reducing antioxidant power (FRAP) and 2,2'-azinobis-3-ethylbenzothiozoline-6-sulfonic acid (ABTS) cation decolorization test] we confirmed the antioxidant potentials of stigmasterol. Forty-eight C57/BL6 mice were equally divided into four groups (A-D). A; administered saline, B; vanadium (sodium metavanadate [NaVO3]), C; stigmasterol and NaVO3, and D; stigmasterol only intraperitoneally for twenty-eight days. We investigated spatial memory, anxiety, and grip strength in the various treatment groups. Thereafter we examined the brain samples for neuroinflammatory markers, levels of antioxidant enzymes (SOD, GPx, GSH), NG2, PDGFα myelin proteolipid protein, myelin basic protein, and astrocytic expression of GFAP. RESULTS: Our data revealed a high radical scavenging activity by stigmasterol in the various radical systems. Animal studies revealed increased activities of in vivo antioxidant enzymes, decreased lipid peroxidation, and oxidative stress markers when stigmasterol was co-administered with NaVO3 in mice

hippocampal homogenates. Similarly, the cognitive and motor coordination deficits, downregulation of matured oligodendrocytes, and oligodendrocyte precursor cells in the NaVO3-only group were rescued with concomitant administration of stigmasterol. CONCLUSIONS: These results show the potential of stigmasterol in modulating vanadium-induced neurotoxicity and promoting remyelination by enhancing the proliferation of oligodendrocyte precursor cells.

PS01.04: Myelin in aging and cognitive impairment

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Cerebral small vessel disease (cSVD) is the second most common cause of cognitive impairment and dementia. At a macrostructural level, cSVD predominantly manifests as white matter hyperintensities. At a microstructural level, pathology studies report myelin damage as a salient feature. Myelin water imaging is a quantitative magnetic resonance imaging technique that uses a multi-echo T2 relaxation sequence; it is the gold-standard technique for measuring myelin content in-vivo. Myelin water imaging can provide more myelin-specific tissue characterization, but this technique has yet to be applied to people with cSVD. Consequently, the specific role of myelin content in cSVD cognition is poorly understood. To better understand the role of myelin in cognitive impairment, this presentation will aim to: 1) review the basic concepts of myelin water imaging and its role in understanding cognitive impairment and dementia; 2) review age-related myelin alterations and; 3) review data assessing the association between myelin content and cognitive function in people with cSVD.

Parallel Symposium 02: Neural mechanisms of skilled motor control across species, circuits, and behaviors

PS02.01: Cell types and networks for spinal motor control

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BACKGROUND AND AIM: To understand how mammalian behaviors are enacted, we focus on the final point of neural control over movement: the spinal cord. This critical region of the central nervous system contains the motoneurons that command the muscles of the body, the premotor neurons that are, in turn, the primary regulators of motoneuron activity, and the broad spinal networks that can autonomously orchestrate many movements even without input from the brain. Our long-term aims are (1) to define and characterize the cell types and pathways of the spinal cord and (2) to ask how specific aspects of motor control are instantiated in specific neuroanatomical substrates. METHODS: We used two complementary approaches to study spinal cord function: characterizing spinal neuron cell types transcriptionally with single cell sequencing and charting their dynamic neural activity during behavior with high density electrophysiological recordings. RESULTS: We found that spatial distribution along the dorsal-ventral axis is the primary determinant of spinal neuron relationships. In both mouse and human adult spinal cord, transcriptional dorsal neural types were discrete, robust, and characterized by well-defined molecular signatures. In contrast, ventral types were closely related, less robust, and displayed

overlapping gene expression. We also found that, in the adult mouse spinal cord, dorsal neurons showed many different activity patterns during walking behavior, while ventral neurons displayed low-dimensional population activity. CONCLUSIONS: We propose that the spinal cord contains at least two distinct organizational strategies that relate neuronal diversity to functional mode. In the dorsal horn, neurons can be divided into distinct types that may carry out specialized or discrete sensorimotor functions, while in the ventral horn neurons may operate as a broad population to execute rhythmic locomotion.

PS02.02: Somatosensory predictions are directly embedded in neural activity that controls movement

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When moving through the environment, we often encounter unexpected external forces that need to be countered to ensure successful motor behaviour. Because sensory feedback from mechanoreceptors in the skin and muscles, which ultimately signal the nature of these external forces, is often too slow to act upon directly, the nervous system may rely on prior information about the environment to make predictions about possible external forces and thus hasten and improve its responses. Imagine riding a bike down a trail, visual information about upcoming rocks may not let you perfectly predict if you will hit a rock and how you will need to correct your steering if you do, but it will likely narrow down the range of possible steering corrections which can improve your response if and when its needeed. It is unknown how such somatosensory priors arise in the nervous system and how they interact with ongoing motor control processes. In this talk, I will describe our recent studies in humans and macaque monkeys where participants were engaged in a postural control task while being provided with explicit or implicit information about the probability distribution from which the direction of upcoming mechanical perturbations would be drawn. That is, the participant was given probabilistic information about how their postural control would be challenged by a mechanical perturbation if it happened. Humans readily integrated probability cues with minimal training and on single trials, showing appropriate shifts in muscle activity within 70 ms of perturbation onset, substantially faster than the time it takes to initiate a voluntary movement. With training, monkeys showed the same capacity to integrate somatosensory priors into their rapid muscle responses at latencies faster than typical measures of voluntary reaction time. High-density single neuron recordings using Neuropixel probes revealed a robust signature of somatosensory predictions in the prefrontal, premotor and motor cortices, but not in the somatosensory cortex. An artificial neural network trained to perform a range of reaching behaviors with a biomechanically realistic model of the arm also learned to produce somatosensory predictions where possible and produced behaviour, muscle activity and neural responses very similar to the empirical studies. Our work uncovers a direct link between sensory predictions and motor control processes -- populations of neurons working together to counter mechanical perturbations are systematically biased by somatosensory predictions about mechanical perturbations in a way that lets the brain effectively respond immediately when a perturbation is detected but before the details about the perturbation are fully resolved.

PS02.03: Dynamical mechanisms of flexible pattern generation in spinal neural populations

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Recent investigations into the coordinated activity of neuronal populations in motor circuits have revealed low-dimensional dynamical features hypothesized to support the generation of patterned motor output. However, such studies have typically relied on vast simplifications - trial-averaging, heavy smoothing - and are often far removed from muscle activity, the true output of the motor system. Thus it is unclear whether the uncovered dynamical features are primarily useful for intuition-building, or reflect computational mechanisms that operate at the temporal precision of motor control. Here we investigated the neural population closest to motor output - spinal interneurons - and tested the degree and temporal precision with which low-dimensional spinal dynamical features reflect the generation of muscle activity. We studied lumbar intermediate zone interneuronal population activity and bilateral, multi-muscle intramuscular EMG recorded in two decerebrated T9 spinalized cats performing air-stepping. We uncovered dynamical features using AutoLFADS, an unsupervised deep learning method to infer latent dynamics from neural and muscle population recordings. Spinal population dynamics were highly predictive of multi-muscle activity on individual gait cycles on a millisecond timescale. However, the reverse was not true: the spinal activity was higher dimensional than muscle activity and contained features not directly related to muscle output. We hypothesized that spinal populations may use these higher dimensions to separate internal timing mechanisms from motor output. Specifically, we investigated extensor burst duration during the gait cycle, which varied step to step based on locomotion speed. We uncovered oscillatory dynamics within the spinal population activity, and found that the duration spent within the oscillator was highly predictive of single-gait cycle variations in extensor burst duration, precise to within tens of milliseconds. These results reveal low-dimensional dynamical features in spinal interneuron activity that may be integral in enabling flexible pattern generation and for precisely controlling timing variations in motor output.

PS02.04: Learning and refining skilled actions in the basal ganglia forelimb circuitry

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BACKGROUND: When a novel action is learned from reinforcement, the brain assigns credit to the movement that led to reward and refines it to a precise skill. For complex actions, there are different movements that can lead to reward, and the aspects of movements that are initially explored may determine what is learned. METHODS: We developed a behavior task to study the refinement of a skilled action, and probe the content of what is learned. Head-fixed mice produce complex forelimb trajectories with a 2D joystick as they learn to move it from a set start position to a rewarded target area. As animals learn this skilled action, credit may be assigned to different aspects of the movement such as the correct initial trajectory direction, or the or the limb position at target entry. RESULTS: At first, successful joystick trajectories (hits) are variable in their initial direction, tortuosity, and inter-trial spatial directionality

measured by vector field analysis. With learning, the hits are refined in these movement aspects. To probe what has been reinforced, we move the joystick start position to the left or right in catch trials while maintaining the target position, testing if animals learned to move in a specific direction or to a specific endpoint. We find that some animals move in the same initial direction from all starts (direction learners), while other animals guide the joystick into the target from the new starts by correcting their direction (endpoint learners), indicating that different movement aspects were reinforced in different animals. Furthermore, the degree to which an animal showed direction vs endpoint learning correlated with the inter-trial directional variability early in training, suggesting that the initial behavior affects what is reinforced. Lesioning the sensorimotor cortex specifically decreased inter-trial directional variability, pointing to a role for cortex in the generation of variable movements that are reinforced in learning. This cortical motor command is thought to be reinforced in striatum through dopamine, inducing plasticity and allowing the reselection of that command. But how are different aspects of the movement encoded? Motor cortex contains different cell classes, particularly corticospinal neurons (CSpn) with striatal collaterals and intratelencephalic corticostriatal (IT-CStr) neurons. Using 2-photon calcium imaging and linear decoding methods, we found that an ongoing hand position command is conveyed particularly by CSpns. Additionally, we find that an initial direction command is conveyed by thalamus to striatum and lesioning this area distinctly impairs the refinement of the initial movement direction. CONCLUSIONS: These findings suggest that animals learn different aspects of a skilled action depending on their initial exploration behavior. Further, distinct pathways of the corticostriatal and thalamic circuitry may convey these aspects of the action to be reinforced in striatum.

Parallel Symposium 03: New approaches for human stem cell models of neurological disorders reveal mechanisms and therapeutic strategies

PS03.01: Investigating neural circuitry abnormalities at cellular resolution in human 3D organoid models of brain development disorders

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The 15q13.3 microdeletion syndrome is a common genetic disorder associated with multiple neurodevelopmental conditions such as autism spectrum disorder, schizophrenia, and epilepsy. The cellular, molecular and developmental aetiologies that contribute to this syndrome remain unknown. In this presentation, we will highlight our previous findings that postnatal cortical excitatory neurons are a vulnerable cell type, which is common to other neurodevelopmental disorders. However, the late-stage screening leaves a considerable gap in our understanding of what may be early prenatal deficits that give rose to postnatal developmental impairments. Therefore, we are using unguided (cerebral) and region-specific forebrain organoids derived from 15q13.3 deletion families to identify critical windows and vulnerable brain cell types and regions throughout prenatal development that may precede postnatal impairments. Using bulk and scRNA sequencing at multiple timepoints, we are profiling the developmental trajectory of this disorder, and have identified early growth abnormalities, maturation impairments in newborn neurons, as well as global disruptions in cell-cell signaling. To understand the

effects of perturbed maturation on neural circuitry, we generated sparsely labeled dorsal-ventral forebrain assembloids and found impaired migration of ventral inhibitory neurons. Lastly, we are combining this approach with spatial and scRNA sequencing to identify affected cell types and cytoarchitectural changes within the 15q13.3 assembloid system. In summary, we hope that our combination of cell type characterization, pathway identification, and circuitry phenotyping will provide a thorough understanding of how the 15q13.3 microdeletion disorder impairs prenatal and postnatal development, an approach that could be applied to other genetic NDD models to understand pathophysiological mechanisms.

PS03.02: Altered proteostasis in fragile X syndrome and other neuropsychiatric disorders

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BACKGROUND AND AIM: Autism spectrum disorders (ASDs) are complex, multifactorial disorders clinically characterized by social and behavioral phenotypes. Several features of autism are also seen in other neuropsychiatric disorders, and a promising strategy to elucidate this shared neurobiology is the study of single-gene causes such as fragile X syndrome (FXS), the most common heritable cause of autism and intellectual disability. Loss of expression of the RNA-binding protein FMRP leads to defects in protein synthesis, signal transduction and neuronal circuit function. Notably, these are key phenotypes shared by other neurological disorders, including schizophrenia, and epilepsy. Large-scale transcriptomic studies and classical biochemical methods have enabled the discovery of candidate pathways and targets that may underlie cellular and molecular phenotypes in these disorders. While these studies have provided invaluable insight, single-target strategies have not translated into effective therapies in a clinical setting. Here, we aim to use human patient induced pluripotent stem cell (iPSC)-derived organoids to study the altered developmental proteome and translatome in fragile X syndrome. To date, a quantitative analysis of the disease-relevant, human-specific brain proteome is lacking. Proteins are the effectors of the transcriptome and altered proteostasis is understudied in human models of neuropsychiatric disease. METHODS: Here, we use novel techniques to profile the nascent and steady state proteome during early human brain development. We have established methods to generate cortical organoids from iPSCs in our lab (n= 3 CTR, 4 FXS), and harvested organoids at three early developmental timepoints. We used tandem mass tagging (TMT) and Bioorthogonal Non-Canonical Amino acid Tagging (BONCAT) followed by mass spectrometry to quantitatively assess proteostasis in patient organoids. We also performed paired RNA sequencing in these samples. Recent advances in bioinformatic tools have allowed for the development of gene expression networks, which organize the transcriptome into functional "modules" that represent major sources of biological variance, including modules enriched in genes expressed by different cell types and those that reflect specific biological and pathophysiologic processes. We used a similar approach to analyze our proteomics and transcriptomics data across iPSC lines from multiple individuals. RESULTS: We have built human brain-specific protein and RNA networks using control and FXS patient iPSC-derived organoids across early development. We have identified modules with strong associations to known pathological and clinical phenotypes. We have further identified disrupted modules that are preserved across other disorders. CONCLUSIONS: Our

novel approaches allow us to define cell-type and developmental stage-specific molecular signatures that are drivers of disease and can be targeted for therapeutic intervention.

PS03.03: Identifying the neurodevelopmental impact of the 3q29 deletion through single-cell sequencing

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BACKGROUND AND AIM: The 3q29 deletion (3q29Del) is the strongest identified genetic risk factor for schizophrenia, but the cellular and molecular effects of this allele on human neurodevelopment have not been identified. METHODS: To systematically investigate 3q29Del effects on gene expression, we performed single-cell mRNA sequencing in two model systems with complementary advantages: human cortical organoids from isogenic 3q29Del induced pluripotent stem cell lines and perinatal isocortex from syntenic 3q29Del mouse brain. To test transcriptomic predictions, we performed immunoblotting on Percoll-isolated mitochondria from mouse brain and Seahorse mitochondrial stress assays on human engineered cell lines. RESULTS: We observed consistent patterns of dysregulated gene expression related to mitochondria and cellular metabolism, which were supported by findings of disrupted stoichiometry of oxidative phosphorylation complex proteins in mouse brain and altered mitochondrial function in human 3q29Del cell lines. CONCLUSIONS: Our findings indicate that the 3q29Del disrupts mitochondrial function and metabolic flexibility, which may have neurodevelopmental consequences.

PS03.04: Drug screens of human induced Pluripotent Stem Cell (hiPSC) derived neuronal networks on multi-electrode arrays

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Neurological disease modeling and drug discovery efforts would greatly benefit from human cell-based platforms to study neuronal networks and synaptic plasticity. Using human induced pluripotent stem cell (hiPSC)-derived neurons, we have developed a multielectrode array (MEA) assay in multi-well formats that recapitulates physiologically relevant synchronized bursting properties sensitive to shifts in excitation/inhibition balance. We have performed two screens of this assay against 280 compounds in dose response, one against compounds that modulate channels and neurotransmitter receptors, and the other against potential neurotoxic chemicals, leading to a compendium of data signatures associated with pharmacological manipulation of network dynamics. In addition, we have used this assay to develop approaches to investigate synaptic plasticity, an essential step towards establishing relevant disease models. To investigate long-term potentiation (LTP) in the system, we used a chemical LTP (cLTP) paradigm to increase cAMP levels. Importantly, this label-free, non-destructive approach on MEAs, enables tracking of the late phase of LTP for days after induction. We observed that cLTP results in increased firing and network bursting frequencies that last for up to 72 hours after drug washout. In a demonstration of how the system can be manipulated using pharmacological and other blocking reagents to probe underlying molecular mechanisms, we showed these effects are largely independent

of the NMDAR and partially dependent on BDNF, and other unidentified factors released into the medium. Finally, we observed molecular hallmarks of LTP, including induction of activity-regulated gene expression. We are also using MEAs to develop models of synaptic scaling, a form of homeostatic plasticity, where we show that chemical induction that chronically increases or decreases activity induces compensatory mechanisms and a return to baseline activity. In summary, the assays we have developed offer the opportunity to perform drug screens and investigate different forms of plasticity on hiPSC neuronal networks, a powerful approach in the context of human genetics reflected by hiPSC models of neurological disease.

Parallel Symposium 04: Form dictates function: crosstalk between channels, scaffolds, and the cytoskeleton with implications for nervous system development and disease

PS04.01: UNC-9/Innexin locally inhibits chemical synapse formation independent of its channel activity in C. elegans

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In the nervous system, neurons communicate with their target cells via specialized cell-cell interfaces called synapses. Precise functioning of the nervous system requires that the number and position of synapses are tightly regulated. This regulation is achieved by various signaling and cell surface proteins. Abnormal synapse number, position, and function cause miscommunication between neurons and their target cells, which underlie several neurological disorders. For example, excessive synaptic connections occur in Autism Spectrum Disorder, and excessive excitatory synapses are also observed in the mouse model of epilepsy. There are two types of synapses in the nervous system: chemical and electrical synapses. Chemical synapse is an asymmetric cellular interface where presynaptically released neurotransmitters bind to receptors on postsynaptic specializations called dendritic spines. Electrical synapse or gap junction is a symmetric interface consisting of tetra-membrane spanning proteins, connexins (Cx) in mammals, and innexins (INX) in invertebrates. In mammals, there is another family of gap junction proteins called pannexins (PANX), which share sequence homology with INX. Despite no sequence similarity between Cx and INX, recent cryoelectron microscopy revealed a surprising structural similarity between mammalian Cx26 and C. elegans INX-6. Connexins and innexins form multimers (hexamers or octamers) on neighboring cells that dock together to form gap junctions whereby neurons are electrically coupled via the exchange of small molecules and ions. While gap junction proteins function primarily as channels, growing evidence supports channel-independent roles for gap junction proteins as cytoskeletal regulators. For example, human Cx43 controls the migration of B lymphocytes via Rap1 small GTPase independent of its gap junction channel activity. Functional and structural interactions between chemical synapses and gap junctions have been observed in many aspects of neurodevelopment and function, yet their molecular mechanisms are largely unknown. Here we show a novel role for a gap junction protein in controlling tiled synaptic arrangement in the GABAergic motor neurons in Caenorhabditis elegans, in which their axons and synapses overlap minimally with their neighboring neurons within the same class. We found that while EGL-20/Wnt controls axonal tiling, their

presynaptic tiling is mediated by a gap junction protein UNC-9/Innexin, that is localized at the presynaptic tiling border between neighboring dorsal D-type GABAergic motor neurons. Strikingly, the gap junction channel activity of UNC-9 is dispensable for its function in controlling tiled presynaptic patterning. While gap junctions are crucial for the proper functioning of the nervous system as channels, our finding uncovered the novel channel-independent role of UNC-9 in synapse patterning.

PS04.02: Cytoskeletal rearrangement promotes neuroprotection following excitotoxicity at the periphery of the dendritic arbour

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During a stroke, disrupted regional blood flow creates an anoxic and nutrient-deficient core triggering elevated extracellular glutamate, excitotoxicity, and neuronal death. Although we and others have determined the mechanism through which neurons in the stroke core inevitably die, it remains unclear why neurons in the neighbouring hypoperfused brain tissue (penumbra) have less predictable outcomes. Penumbral neurons can appear structurally normal yet branches from these neurons that cross into the core undergo a dramatic structural change forming dendritic varicosities, "blebs". We hypothesized that a protective mechanism exists at this core-penumbra interface to not only prevent the spread of blebbing, but to also prevent propagation of excitotoxicity within the partially injured neuron. To address this, we created an in vitro model of the core-penumbra interface, using focal photo-lysis of caged NMDA - "focal excitotoxicity", that targets isolated peripheral branches in the dendritic arbour to allow interrogation of molecular mechanisms underlying this observed directional blebbing. Here, following focal excitotoxicity, neurons sequester cytotoxic calcium in blebs of targeted 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 tourniquet formation is prevented, the neuron dies; yet, when maintained, the damaged branches either pinch off or recover, promoting cell survival. We introduce a novel neuroprotective mechanism that could be bolstered to preserve penumbral brain tissue with the goal of improving stroke-related patient outcomes.

PS04.03: Synaptopodin, an actin-associated protein, is required for long-term depression

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The remarkable ability of the central nervous system to adapt, learn, and form memories is considered to be based on activity-dependent modifications of synaptic connections. At excitatory synapses dendritic spines are poised to be the major site of these activities. They are capable of undergo enlargement, shrinking and even elimination to adapt to changes in synaptic strength. Inability to adapt to perturbances in synaptic activity can lead to cognitive disorders. Despite this knowledge, the molecular processes underlying why certain synapses are more likely to be maintained to provide a physical substrate for long-term information storage while others are more structurally plastic are poorly understood and remains an important area in neuroscience research. This leads us to the question are

there specific protein(s) or structure in dendritic spines that act as "gate keeper" for permitting individual synapses to undergo changes in synaptic strength. 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. Moreover, SP is dysregulated in neurological disorders with synaptic perturbation such as Alzheimer's disease and Fragile X syndrome. Understanding the neuronal and synaptic function of SP could lead to potential therapeutics for these disorders. But, to date, it is not clear if SP is a requirement for long-term depression (LTD), either NMDAR-LTD or mGluR-LTD. Here, I will show that expression of SP is required for normal induction of both forms of LTD at the CA3-CA1 excitatory synapses of mice. First, we induced NMDA-LTD by low frequency stimulation as well as a more physiological protocol. Both protocols revealed a lack of NMDAR-LTD in a mice model lacking SP (SPKO) compared to WT. Then, we also assessed the expression of mGluR-LTD, a type of LTD that is mechanistically different from NMDAR-LTD. We found that mGluR-LTD is impaired in SPKO compared to wildtype. Through pharmacological interventions, we also pinpointed the metabotropic glutamate receptor affected by the loss of SP. Together, our results highlight the importance of SP for long-term depression at CA3-CA1 synapses.

PS04.04: Pannexin 1 regulates spine stabilization by sequestering spine cytoskeletal regulators

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BACKGROUND AND AIM: Neurons receive excitatory input at microscopic cytoskeleton-rich structures called dendritic spines. Spines develop from highly dynamic protrusions that undergo stabilization. Spine instability and loss is common to several developmental and neurodegenerative conditions; however, limited understanding of the underlying mechanisms hinders translation. We recently discovered that the levels of the pannexin 1 channel-forming protein and signaling hub in mouse cortical neurons decrease dramatically just prior to peak dendritic spine formation, and accordingly, neuronal pannexin 1 inhibits dendritic spine stability. Relatedly, we discovered pannexin 1 interactions with cytoskeletal regulators needed for spine stabilization and maturation, but how these interactions regulate spine stabilization remains unclear. Importantly, pannexin 1 and its interacting proteins are linked to several neurological disorders associated with spine instability and loss, but their precise role(s) in these conditions are unresolved, underscoring the need for further study. Notably, we also discovered that elevated extracellular ATP triggers pannexin 1 internalization in Neuro2a cells, but whether a similar mechanism is implicated in developmental downregulation of neuronal pannexin 1 is unknown. To this end, we are investigating the molecular mechanisms underlying pannexin 1 inhibition of spine stability and pannexin 1 proteostasis in cortical neurons. We hypothesize (1) that neuronal pannexin 1 is a developmental brake preventing premature spine stabilization by sequestering key cytoskeletal regulators, and (2) that extracellular ATP regulates proteostasis of neuronal pannexin 1. METHODS: To begin to address these hypotheses, we use a combination of biochemical tools and live and fixed

confocal and stimulated-emission depletion microscopy in vitro and in situ. RESULTS: Treatment with drugs and peptides designed to disrupt pannexin 1 interactions with cytoskeletal regulators increases spine density. Studies on the impact of modulating extracellular ATP on pannexin 1 levels in neurons are on-going. CONCLUSIONS: The outcomes of this work will enhance understanding of pannexin 1 regulation of dendritic spines in health and disease and provide a foundation for the development of therapeutic approaches to improve spine stability based on pannexin 1.

Parallel Symposium 05: Interactions between diet and cognition

PS05.01: Trapping a meal engram in the ventral hippocampus

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Work conducted in both humans and rodents reveals learning and memory function influence eating behaviours. The ventral hippocampus (HPCv) is known to regulate both mnemonic processes and food intake, yet the neural mechanisms mediating this integration have not been systematically evaluated. We set to illustrate the activity dynamics of HPCv neurons during appetitive and consummatory behaviours and to characterize the profile of HPCv neurons engaged by food consumption in adult male Sprague-Dawley rats. [1] Fiber photometry-based recording of dynamic bulk HPCv calcium-dependent activity in awake behaving rats revealed increased activity during a foraging-based spatial memory task and during inter-bout intervals in an ad libitum feeding session. Engagement of HPCv neurons during the ad libitum feeding session was predictive of performance in the foraging-related spatial memory task. [2] To evaluate a possible functional connection between HPCv neurons engaged by eating and foraging-related spatial memory, a targeted recombination in active population viral approach was used to induce diphteria toxin-mediated ablation of HPCv neurons engaged in a 'Fasted' or 'Fed' state. Results show that ablation of HPCv food-responsive neurons selectively impairs spatial memory in the context of foraging. [3] To identify the projection profile of HPCv food-responsive neurons, a similar targeted recombination approach was used to express green fluorescent protein in HPCv neurons engaged in a 'Fasted' or 'Fed' state. Presence of axonal projections from the HPCv to the lateral hypothalamic area (LHA) was specific to rats from the 'Fed' condition. [4] To confirm the relevance of this neural pathway to the function of HPCv food-responsive neurons, rats expressing inhibitory chemogenetic receptors (hM4Di) in HPCv-to-LHA neurons received intracerebroventricular infusion of clozapine-N-oxide or its vehicle. Acute silencing of HPCv-to-LHA neurons impaired performance in the foraging-related spatial memory task. [5] To characterize the genetic profile of HPCv food-responsive neurons, single-nucleus RNA sequencing was performed on HPCv microdissections harvested in a 'Fed' or 'Fasted' state. Results identify that HPCv food and fast-responsive neurons present distinct molecular profiles, with those engaged in a 'Fed' state being enriched in the serotonin receptor type 2a. [6] To functionally validate this genetic profile, rats received bilateral HPCv infusion of a serotonin type 2a receptor antagonist or its vehicle. HPCv antagonism of serotonin type 2a receptors also impaired performance in the foraging-related spatial

memory task. Together, these results identify and characterize a population of HPCv neurons that are engaged by eating and contribute functionally to foraging-related spatial memory.

PS05.02: Obesogenic diet induces circuit-specific memory deficits

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Obesity is associated with neurocognitive dysfunction, including memory deficits. This is particularly problematic during adolescence, which represents a crucial period for maturation of brain structures controlling memory, such as the hippocampus (HPC). Using rodent models, we demonstrated that obesogenic high-fat diet (HFD) intake during adolescence, but not at adulthood, impairs spatial, relational and object-based memory, despite similar overweight and metabolic disturbances at both periods of HFD exposure. Surprisingly, we recently found that these deficits in object-based memory are associated with higher HPC activation (i.e. Fos expression) after training. Interestingly, decreasing HPC activity by manipulation of neuromodulatory systems (such as endocannabinoid or glucocorticoid systems) or chemogenetic inactivation of glutamatergic projecting neurons in ventral HPC reversed memory deficits in HFD-fed subjects. Focusing on the potential role of HPC efferent pathways, we established that HFD enhanced activation of ventral HPC projections to either nucleus accumbens or medial prefrontal cortex after training. Using an intersectional viral approach, we revealed that specific chemogenetic inactivation of the ventral HPC-nucleus accumbens pathway rescued HFD-induced deficits in recognition, but not location, memory. Conversely, inactivation of the ventral HPC-medial prefrontal cortex pathway restored location, but not recognition, memory impairments produced by HFD. Either pathway manipulation did not affect exploration, locomotion or anxiety-like behaviour. These findings suggest that HFD intake throughout adolescence impairs different types of memory through overactivation of specific hippocampal efferent pathways and that targeting these overactive pathways has therapeutic potential.

PS05.03: How an obesogenic high-fat diet disrupts oxytocinergic signaling in hippocampal area CA2 and social memory formation

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Obesity is well-known to have detrimental effects on diverse cognitive functions and in particular, hippocampal-dependent memory processes are compromised. We found that an obesogenic high-fat diet (HFD) during adolescence/early adulthood results in impaired social memory formation without changes in sociability. This result is reminiscent of the behavioral phenotype observed following selective lesion of hippocampal CA2, prompting us to examine the effect of HFD intake on the cellular properties and synaptic transmission in this region. We found that 12 weeks of HFD (starting at weaning) induces increased synaptic transmission between CA3-CA2 pyramidal neuron (PN) synapses and EC-CA2 synapses. Strikingly, we found that reducing CA2 PN transmission using inhibitory DREADD expression specifically in CA2 PNs completely restored social memory formation. In humans and animal models,

HFD is known to alter the oxytocinergic (OT) system and results in a decrease in both OT levels and OT receptor mRNA expression in the hippocampus. We found that while a transient application of OT strongly increased excitatory transmission onto PNs in control-fed mice, OT receptor activation had no effect on synaptic transmission in HFD-fed mice. Furthermore, we found that in control conditions, a brief application of OT is permissive for the induction of an endocannabinoid-mediated depression of inhibitory transmission. This plasticity results in a large increase in the excitation/inhibition ratio at CA3 inputs and we have previously shown that endocannabinoid-mediated plasticity is induced during social interaction and is required for social memory formation. Interestingly, in HFD-fed mice, OT application does not facilitate the induction of endocannabinoid-mediated plasticity. Thus, this mechanism likely explains the deficit in social memory formation in HFD-fed mice. Therefore, these results describe specific alterations in hippocampal area CA2 following HFD intake and reveal how HFD-induced alterations in the oxytocinergic system might underly the deficit in social memory formation.

PS05.04: Time dependent changes in the orbitofrontal cortex with exposure to an obesogenic diet

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BACKGROUND AND AIM: The global obesity pandemic is associated with a transition in the consumption of traditional foods to highly marketed, inexpensive, energy dense, palatable foods. It has been proposed that the increased availability of these foods usurps an individual's ability to make decisions and control its caloric intake leading to overconsumption and obesity. However, it is unclear how the current obesogenic environment interacts with decision-making processes to influence and bias choices about our feeding behaviour. The lateral orbitofrontal cortex (lOFC) receives sensory information about food and integrates these signals with expected outcomes to guide future actions, and thus may play a key role in a distributed network of neural circuits that regulate feeding behaviour. Here, we will present evidence for a role of the lOFC in the cognitive control of feeding behaviour in obesity. METHODS and RESULTS: Using patch clamp electrophysiology, obese mice exhibited decreased inhibitory synaptic transmission and disinhibition of lOFC pyramidal neurons. This was associated with impaired reward devaluation in obese but not lean mice. Using inhibitory DREADDS expressed in GABAergic neurons, disinhibition of lOFC pyramidal neurons lead to impaired reward devaluation, suggesting that obesity-induced disinhibition may underly impaired reward valuation. Therefore, we used optogenetic and pharmacological (NNC-711, a GABA transporter inhibitor) strategies to boost GABAergic tone and restore excitability in the lOFC and this restored goal directed behaviour. We also examine the time course of synaptic changes and identify that changes in tonic inhibition resulting in disinhibition of pyramidal neurons occurs early on in diet exposure. CONCLUSIONS: Taken together, these results suggest that an obesogenic diet disinhibits the OFC, which may influence cognitive and emotional processing of the value representation leading to overeating associated with obesity.

Parallel Symposium 06: Synaptic, molecular and ultrastructural dynamics during learning

PS06.01: Machine learning-assisted super-resolution microscopy of molecular interactions in the brain

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BACKGROUND: Understanding the molecular mechanisms underlying synaptic transmission is challenging in part because synapses are tiny (less than a micron), exhibit a wide range of shapes and internal structures, undergo activity-dependent plasticity, and their molecular components are dynamic. We must be able to observe the molecular dynamics and interactions of synaptic proteins at their scale: the nanoscale. Super-resolution microscopy (or optical nanoscopy) techniques allow characterizing molecular interactions inside living cells with unprecedented spatiotemporal resolution. These techniques come with several layers of complexity in their implementation. This has limited their adoption as well as their adaptability to multi-color, multi-modal, and long-term imaging in living neurons. Developing machine learning (ML) assisted frameworks for optical nanoscopy allows real-time optimization of multi-modal live-cell imaging at the nanoscale as well as for quantitative high throughput super-resolution image analysis. METHODS: We have developed machine and deep learning approaches for: 1) quantitative analysis of neuronal protein organization in optical nanoscopy images, and 2) the optimization of image acquisition schemes, especially in living neuronal samples. RESULTS: Combining statistical analysis approaches with unsupervised machine learning allowed us to identify synaptic subtypes and describe how their organization and morphology is affected by synaptic activity. Using this quantitative analysis strategy we measured at the synapse population level, that treatments driving synaptic potentiation cause an increase in the degree of association of pre- and post-synaptic nanodomains, whereas a stimulus driving synaptic depression had an opposite effect. To truly investigate activity-dependant remodelling of neuronal proteins at the nanoscale, the optimization of optical nanoscopy approaches to minimize their invasiveness is required. We integrated generative deep learning approaches in the acquisition loop of an optical super-resolution microscope to guide the image acquisition process and reduce the light exposition on the sample. This allowed us to perform time-lapse imaging of protein reorganization at the nanoscale in living cultured neurons. CONCLUSION: We use machine learning-assisted microscopy to characterize activity-dependent remodelling of neuronal proteins. Our approaches not only automate image analysis but also increase multi-dimensional analysis performance of synaptic nanostructures. The development of machine learning-based analysis tools is transforming our ability to discover and characterize rare phenomena that may influence these synaptic connections and thus to discover new mechanisms influencing the proper functioning of our brain.

PS06.02: Nature and dynamics of synaptic eligibility traces in cortex

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Learning and memory processes are fundamental to survival in dynamic environments. The ability of synapses to undergo associative, activity-dependent and long-term alterations in their weights lies at the crux of current cellular models of learning. However, canonical forms of Hebbian plasticity, such as spike-timing-dependent plasticity, typically require hundreds of repetitions and are inherently reflecting the correlation detection of cellular events occurring over time scales (tens of milliseconds) that are

fundamentally distinct to those of behavioural associative learning (at least hundreds of milliseconds). Eligibility traces, a theoretical construct developed and widely used in machine learning, can be conceptualized as a silent process that keeps a time-decaying record of a synapse's activity, tagging it for weight update by a delayed instructive signal. As such, they have been suggested to solve the temporal credit assignment problem proper to reinforced learning. Yet, their existence and material nature have not been conclusively established. I will present data that shows that the pairing, in indiscriminate order, of pre- and postsynaptic events with behaviourally relevant temporal delays induced synaptic potentiation in layer 5 pyramidal neurons of mice prefrontal areas. Two-photon (2P) uncaging and Calcium (Ca2+) imaging experiments further highlighted a spatially-constrained, latent plasticity of Ca2+ dynamics that was mediated by dendritic ER Ca2+ stores, and enacted an effective state-dependent switch in ER function. This switch temporarily held a memory of previous cellular activity and participated in instantiating synaptic weight updates by a delayed instructive cue, and thus satisfied the features expected of an eligibility trace. These results thus collectively describe a mechanism that account for how individual neurons, as opposed to networks, can conjunctively bind cellular events that are separated by behaviorally relevant temporal delays and thus offer a heretofore lacking cellular model of reinforced learning.

PS06.03: Heterogeneity in information processing by cerebellar synapses

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The cerebellum supports varied functions, from motor learning to cognitive tasks. Yet, the cytoarchitecture of the cerebellar cortex is remarkably uniform, with a "crystalline" organization of the same circuit structure repeating across lobules. This homogeneous circuitry has led to the understanding that the same computation is performed by different regions of the cerebellar cortex, albeit in the context of different functions. However, previous results suggest that this homogeneity is overlaid by differences in synaptic plasticity in functionally different regions. Specifically, the rules that guide the induction of plasticity at parallel fiber to Purkinje cells synapses vary based on the timing of the specific error signal each region receives. Thus, the timing of plasticity is well-aligned with the behavioral requirements of each local circuit. Nevertheless, parallel fiber synapses, which are the major synaptic input to Purkinje cells, are themselves thought to have similar timing properties across the cerebellum. Here, we investigated the mouse cerebellar cortex using a combination of patch-clamp recordings in acute brain slices and analysis of gene and protein expression. Our focus was on the timing properties of parallel fiber synapses, across functionally and molecularly different regions of the cerebellum. This is particularly relevant to cerebellar function because parallel fibers are the major input to Purkinje cells, which in turn are the only output neurons of the cerebellar cortex. By stimulating parallel fiber inputs with physiologically relevant stimuli, we observed a remarkable heterogeneity in their properties across different cerebellar lobules. Consequently, the parallel fiber-dependent spiking output from Purkinje cells in different regions of the cerebellum was also highly heterogenous. Thus, the input-output transformation performed by Purkinje cells in response to synaptic input is widely different in functionally different regions of the cerebellum. Strikingly, this heterogeneity was dependent on

signaling pathways downstream of metabotropic glutamate receptor (mGluR) activation. We then identified differences in downstream gene expression patterns that correlate with the heterogeneity in timing. Furthermore, such diversity in mGluR-dependent signaling had some overlap, as well as clear distinctions, from the well-established zebrin patterning that is a known basis for molecular heterogeneity in the cerebellum. Overall, we have identified a remarkable heterogeneity in cerebellar information processing that results in timing heterogeneity at parallel fiber synapses.

PS06.04: Role of posttranslational palmitoylation in synaptic plasticity

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Palmitoylation is the most common post-translational lipid modification in the brain. It involves the addition of the fatty acid, palmitate, onto substrate proteins and is exceedingly important for protein trafficking and cell signaling. While ~35% of all proteins in the genome are substrates for palmitoylation, a striking 66% of all synaptic proteins can be palmitoylated. Using proteomic analysis, we identify a list of synaptic proteins that are differentially palmitoylated in the hippocampus of mice that have undergone fear conditioning and demonstrate that the dynamic palmitoylation of proteins is important for the establishment of long-term potentiation. This is of clinical relevance as genetic variants in palmitoylating enzymes are associated with brain disorders and as palmitoylation can be altered by environmental factors including diet.

Parallel Symposium 07: Adolescent stress sensitivity and modulation of behaviour across the lifespan

PS07.01: Synaptic maturation of affective learning circuits

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BACKGROUND AND AIM: Early life experiences crucially define cognitive and mental health function throughout life. Childhood and adolescence are the predominant age of onset for the majority of mental disorders and are periods during which key brain areas involved in cognitive and emotional processing, such as the prefrontal cortex (PFC), hippocampus (HPC) and amygdala, are maturing. Anatomical and morphological changes occur in these brain areas during early life, but how such changes influence circuit function and consequently affect behaviour and the onset of mental illness is currently unknown. METHODS: Here, we used viral tracing, optogenetic-assisted patch clamping, and chemo and optogenetic manipulations during behaviour in mice to examine changes in prefrontal cortex afferent and efferent connections and their functional implications across the lifespan. RESULTS: We found age- and sex- dependent changes in the recruitment of prelimbic and infralimbic cortex projections to amygdala to fear learning and extinction in early life. Furthermore, we mapped age-dependent changes in intermediate and ventral CA1 projections to prefrontal cortex, as well as optically-evoked CA1 responses onto prefrontal cortex subdivisions, from postnatal day (P)10 to P60. CONCLUSIONS: Our data establish a timeline for the postnatal maturation of PFC-amygdala and HPC-PFC synapses in a

subdomain- and target-defined manner. Our identification of asynchronous development among these specialized projections consolidates a blueprint for the maturation of prefrontal circuits with critical implications for the emergence of behavior and the influence of intrinsic and extrinsic factors during early life.

PS07.02: Adolescent social isolation disrupts sex-specific developmental profiles of GABA- and glutamatergic gene expression throughout the reward circuitry

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Background: Individuals with reduced social connections have increased risk for substance use disorder. Because adolescence is a period of reorganization of social reward, the effects of adolescent social experience on reward are robust and persistent. Our lab and others have shown that adolescent social isolation (SI) alters addiction-related behaviors and reward-induced transcription in adulthood, but little is known regarding how SI disrupts normative development of the reward circuitry to influence addiction-related behaviors. Methods: We tested the hypothesis that SI disrupts developmental profiles of GABAergic- and glutamatergic-related gene expression in three key reward-associated brain regions (prefrontal cortex - PFC, basolateral amygdala - BLA and ventral hippocampus - vHIP) to influence behavior in adulthood. Animals were isolated from ~postnatal (P)22 - P42 and then group housed until adulthood. Male and female mice were euthanized on the day of isolation (P22), mid-isolation (P32), on the day of rehousing (P42), and on P72. Micropunches of PFC, BLA and vHIP were collected for gene expression (n= 6-8 animals per age/housing condition for a total of ~150 samples per brain region). Expression of 24 GABAergic and glutamatergic-related genes was assessed using RT-qPCR and analyzed using the comparative Ct method. Palatable food consumption was assessed in a subset of animals to determine how SI, specifically during adolescence, might influence adult reward. Results: Preliminary analysis of behavioral endpoints revealed that SI enhanced preference for palatable food in males only. Three-way ANOVA for sex, SI and age revealed main effects or interactions ($p<0.05$) for glutamatergic-related genes encoding AMPA and NMDA-receptor subunits (Gria1 & 2; Grin1, 2a, 2b & 2c) and glutamate transporter (Slc17a6) in all three brain regions. Although region specific effects were observed, post hoc analysis revealed that expression of many glutamatergic-related genes was enhanced by SI in males on P32. However, GABAergic-related genes were only affected in the PFC. Three-way ANOVA revealed a significant Sex X Age X SI interaction for GABAA receptor subunits (Gabra1, Gabrg1; $p<0.05$), GABA transporter (Slc32a1; $p=0.006$) and Gad2 ($p=0.001$). Post hoc analysis revealed a significant decrease in expression on P32 in males. Conclusions: Together these data suggest that SI results in a transient sex-specific enhancement of the excitatory system across much of the reward circuitry. This effect is most pronounced within the PFC as SI results in a concomitant suppression of the GABAergic system. While the expression effects do not persist after the animals are re-socialized, these finding provide an important mechanism by which SI could reprogram the reward circuitry to influence the observed behavioral consequences in adults.

PS07.03: The long-term and intergenerational effects of adolescent stress

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BACKGROUND AND AIM: Adolescence has emerged as a vulnerable period when stressful events can have lifetime consequences. Moreover, the effects of stressful experiences are not limited to those who directly experience the stress; the children of those exposed to trauma are also more likely to develop mental health challenges. We aim to investigate why and how adolescent stress has long lasting and sometimes intergenerational harmful effects. METHODS: Our laboratory performed a chronic predator stress paradigm across adolescent development. For this, male and female stressed mice were exposed to a rat for 30 minutes each day during the early or late phase of adolescence, while controls remained undisturbed. Mice were then tested as adults in a battery of behavioural tests designed to assess anxiety-like and depressive-like behaviours. After testing, male and female stressed mice and controls were bred, and their adult offspring were assessed in the same behavioural test battery. RESULTS: Mice stressed during adolescence exhibit increased anxiety-like behaviours as adults, and stressed female mice also provide less maternal care to their offspring. The offspring of stressed mice display increased anxiety-like behaviours, similar to what was observed in their parents, but they also show increased depression-like behaviours. CONCLUSIONS: These findings in mice parallel human findings suggesting reduced infant care and negative intergenerational consequences following trauma. The implications of biological versus social intergenerational transfer of information will be discussed.

PS07.04: Developmental age and sex interact to scale the effects of stress on fear regulation

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BACKGROUND AND AIM: Stimuli associated with threat (fear cues) are highly salient. It is widely believed that biasing attentional resources to potential threat in the surrounding environment is adaptive for survival, as it can inform appropriate behavioral responding. Yet, when left unchecked, the inability to disengage attention from threat, or attend to alternative indicators of safety, can contribute to fear-related psychiatric disease such as anxiety or PTSD. Our work investigates how developmental exposure to chronic or acute stress alters learning and memory processes directed toward threat. We aim to elucidate how experiences with threat and safety impact later affective regulation in an effort to inform translation to the treatment of fear and anxiety disorders. METHODS: The present experiments were carried out in both adolescent and adult cohorts of male and female C57bl6J mice. In one set of experiments, mice were exposed to chronic unpredictable stress during peri-adolescence or adulthood and tested either immediately or one month later for the ability to learn about an explicit safety cue and engage processes of conditioned inhibition. In a second set of experiments mice were exposed to mild stress in the form of fear conditioning, or alternatively, received safety conditioning alongside fear conditioning, again during peri-adolescence or adulthood. Mice were tested one month later for the ability to engage processes of fear extinction and the presence of anxiety-like phenotypes. RESULTS: Our findings indicate that both chronic and acute stress experienced during peri-adolescence lead to deficits in fear regulation (safety learning, fear extinction) in adult mice. Notably, the emergence of these deficits

is delayed - adolescent mice exhibit unaltered fear regulation following peri-adolescent stress. Moreover, pairing acute stress with explicit safety learning during adolescence mitigates the detrimental impacts of aversive experience for fear extinction in adulthood. This effect was particularly robust in adolescent males. CONCLUSIONS: Intervention early in life, when the brain is still highly plastic, may provide a powerful opportunity to mitigate the adverse impacts of anxiety before it becomes a lifelong affliction. Our findings show initial support for safety learning during adolescence as a method to mitigate the detrimental impacts of aversive experiences for fear regulation in adulthood, though parameters may vary between males and females. Together, this work emphasizes the impact that exposure to affective stimuli (both fear and safety) can have on later affective processing and suggest both age- and sex-specificity in the promise of safety signal-based treatments for fear-based psychiatric disease.

Parallel Symposium 08: Protein synthesis in brain health and disease

PS08.01: Local protein synthesis in axons sustains synapse-specific neurotransmission

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BACKGROUND AND AIM: Neuron typically has elaborated neuronal processes that extend far away from soma. Yet tens of thousands of synaptic proteins are turned over every minute. This raises the question of how proteins are supplied to the synapses in a timely manner. The ability to synthesize proteins locally and rapidly in dendrites is well known for regulating synaptic plasticity. Similarly, axonal translation has emerged as a critical regulator in early development. Yet, due in part to the low experimental accessibility of micron-sized axons in intact synapses, it is unknown whether local translation in mature axons plays a role in neurotransmission of the mammalian central nervous system. We therefore developed new strategies to elucidate this long-standing question. METHODS: Using quadruple patch clamp recordings and 2-photon laser scanning microscopy, the acute effects of translation inhibition on evoked release from layer-5 pyramidal neurons were explored in acute visual cortex slices from postnatal day 11 to 19 C57BL/6 mice. RESULTS: Using whole-cell recordings to manipulate pre- and postsynaptic neurons independently in acute cortical slices, we observed reduced excitatory postsynaptic responses (EPSP) and increased paired-pulse ratio (PPR) after presynaptic blockade with mTOR inhibitor PP242 (EPSP: 75% ± 4%, n = 12, $p < 0.001$; ΔPPR = 0.16 ± 0.05, $p < 0.01$) or M7 cap analog (EPSP: 47% ± 6%, n = 16, $p < 0.001$; ΔPPR = 0.13 ± 0.05, $p < 0.05$), indicating that synaptic release is sustained by mTOR and cap-dependent PS. Presynaptic NMDA receptor blockade suppressed release (EPSP: 65% ± 5%, n = 8) which was occluded by PS inhibitor (100% ± 6%, n = 9, $p < 0.001$), suggesting NMDARs control PS. Using 2-photon laser microsurgery to sever axon from cell body, we showed that axonal PS sustained neurotransmission (EPSP: 55% ± 4%, n = 7, $p < 0.001$). Live imaging of RNA revealed discrete axonal docking sites, suggesting bouton-specific regulation. In agreement, presynaptic PS was important for neurotransmission at synapses from pyramidal cells to pyramidal cells, but not to inhibitory Martinotti cells (63% ± 6%, n = 7 vs. 116% ± 3%, n = 23, $p < 0.001$) or basket cells (55% ± 5%, n = 8 vs. 100% ± 10%, n = 5, $p < 0.01$). CONCLUSIONS: Axonal translation is a fundamental regulatory principle that locally governs information transfer at central synapses and orchestrates excitation-inhibition balance in the neocortex. Protein synthesis has emerged as a promising candidate target for treating neuropathology

such as autism spectrum disorder and Alzheimer disease, yet the focus has historically been postsynaptic. Our results highlight the potential for neuropathology interventions that rely on synapse-type-specific local translation in axons.

PS08.02: Impact of dendritic processing on synaptic receptor glycosylation and function

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Neuronal development and function require secreted growth factors, surface adhesion molecules and synaptic receptors and thus heavily rely on the organelles of the secretory pathway where theses proteins are synthesized and modified by covalent addition of complex sugars, N-glycans. Our work and that of other groups indicate that a substantial fraction of these proteins, notably synaptic receptors, are locally synthesized in dendrites and use unconventional Golgi-independent pathways to reach the neuronal surface. This local processing modifies protein N-glycosylation states and hence regulates receptor chemical composition and function, unraveling a previously unrecognized mechanism controlling the sensing properties and plasticity of the neuronal membrane.

PS08.03: Targeting ERK signaling to treat Fragile X Syndrome and autism

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BACKGROUND AND AIM: Autism is one of the most prevalent neurodevelopmental disorders both in Canada and worldwide. Fragile X Syndrome (FXS) is the most common genetic cause of autism and intellectual disability. Increased activation of extracellular signal-regulated kinase (ERK) signalling in the brain is observed in both patients and animal models of these conditions. It has been proposed to be a critical node, upon which different risk factors and associated intracellular pathways converge and lead to the phenotypic alterations. We hypothesized that selectively targeting this pathway could reverse core condition-modelling phenotypes in animal models of autism and FXS. METHODS: Here we tested a clinically relevant, selective inhibitor of ERK signaling in two mouse models, one for FXS and one for idiopathic autism. RESULTS: We report that treatment with this inhibitor robustly reduced ERK activation in the brain, and reversed core phenotypes in behavioral and electrophysiological domains in both models. Additionally, the inhibitor treatment reduced eIF4E activation, a key translation initiation factor and a downstream target of ERK, in both models. Further analysis revealed that the treatment did not cause apparent side effects, or affect the control animals. CONCLUSIONS: Our data indicated that selectively inhibiting ERK signalling was beneficial in both models. These results further support the notion that dysregulation in ERK pathway causally contributes to the pathophysiology of autism and FXS. They also suggest that selectively targeting ERK signalling could be a new approach for treating these conditions.

PS08.04: RNA metabolism and pathophysiology of brain developmental disorders: Fragile X Messenger Ribonucleoprotein (FMRP) as a paradigmatic factor

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BACKGROUND AND AIM Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and a leading cause of autism. It is due to the silencing of the FMR1 gene coding for an RNA-binding protein, the Fragile X Messenger RibonucleoProtein (FMRP). This protein is part of ribonucleoprotein complexes associated to polyribosomes and is involved in translational regulation. FMRP works mainly as a translational repressor, but in some cases can also enhance translation. By its action, FMRP modulates the expression levels of a large subset of synaptic proteins. Thousands of mRNA targets of FMRP have been identified, modulating dozens of signaling pathways involved in brain development. To date no specific treatment is available for this disorder. Thus, the search for new treatments able to modify the lifetime course of FXS and to improve its prognosis is urgent. With this purpose, during the last years, we used different and complementary approaches to identify new effective treatment for FXS. METHODS We searched for target mRNAs of FMRP by a CLIP (Cross-Link UV Immunoprecipitation) assay in brain cortex and hippocampus during synaptogenesis. Among the targets we identified, we focused our attention on those involved in the homeostasis of cAMP and cGMP and in the homeostasis of Ca2+. RESULTS We studied the role of FMRP on the modulation of the expression of several of its target mRNAs. Among them, in particular we studied the action of FMRP on the metabolism of its target mRNA Phosphodiesterase 2A (Pde2a), coding for an enzyme involved in both cAMP and cGMP homeostasis. In FXS neurons the levels of PDE2A are elevated, resulting in a reduced abundance of both cAMP and cGMP. CONCLUSION Starting on these findings, we identified a new pharmacological target for FXS, based on the specific inhibition of PDE2A that we validated at preclinical level.

Parallel Symposium 09: Cross-disciplinary neuroscience perspectives on autism spectrum disorder

PS09.01: Amygdala subnuclei maturation and the association with anxiety in children and youth with autism spectrum disorder

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Autism Spectrum Disorder (ASD) is associated with difficulties with emotional recognition in others, which can lead to anxiety in social situations. In fact, nearly 85% of children with ASD report anxiety and nearly 40% of children have a comorbid anxiety disorder. Altered development of the amygdala has been associated with anxiety in children with ASD. However, the amygdala is composed of several input and output nuclei that have widespread cortical and subcortical connections. Only recently has it been possible to study the amygdala subnuclei in vivo using magnetic resonance imaging (MRI). In this symposium talk, in a series of longitudinal and cross-sectional studies, the association of amygdala subnuclei maturation in relation to social difficulties and anxiety behaviours in children and youth with ASD will be presented. This work contributes to a growing body of literature concerning the

characterization of the amygdala subnuclei and the association with anxiety in children with ASD, which can aid in identifying brain-based biomarkers and future treatment avenues for this vulnerable group.

PS09.02: Sex considerations in translational ASD research

Olivia Williams[1], Madeleine Coppolino[1], Erin Dawdy[1], Joshua Manduca[1], Colby Perrin[1], Tariq Akhtar[1], Melissa Perreault[1]
[1]University of Guelph

BACKGROUND AND AIMS: Autism Spectrum Disorders (ASD) exhibit prominent sexual dimorphisms in age of onset, prevalence, etiology and presentation, yet the molecular and cellular underpinnings of these differences remain mostly unexplored. In this presentation, we use the valproic acid (VPA) model of idiopathic ASD to first describe evidence of sex differences in cortical neuronal architecture, neuronal activity, oscillatory function, and behaviour, and to discuss the possible molecular and cellular mechanisms that contribute to these differences. Next, early findings elucidating the sex-specific impact of the cannabis-derived cannflavins (CannA or CannB) on these measures will be examined and their potential as a novel pharmacological strategy for symptom management in ASD discussed. METHODS: Using the VPA model of ASD, in Experiment 1, we employed tracing methodologies, protein localization and abundance assays, and neurophysiological recordings in vitro and in vivo to assess differences in cortical neuronal architecture, activity, cell signaling, and/or behaviour. In Experiment 2, the therapeutic effects of CannA or CannB, extracted and purified from hemp, on these measures in primary cortical cultures (1nM or 100nM) or in adolescent rats (0.2 mg/kg, i.p.) were determined. RESULTS: In vitro studies showed that VPA-derived cortical neurons from sexed pups were less complex and showed elevated neuronal activity with greater effect in the female-derived neurons. In vivo, behavioural testing in adolescence revealed sex-specific ASD-like characteristics in the VPA group. VPA-exposed female rats displayed greater anxiety, showed deficits in recognition memory, as well as in social index scores, whereas VPA males exhibited difficulties in location memory and lower sociality. Female VPA rats displayed alterations in cortical low frequency power, however VPA elevated high frequency power in the male rats and lowered high frequency coherence between the cingulate cortex and the hippocampus. Evaluating the impact of cannflavin treatment, sub-chronic CannA or CannB treatment increased dendritic branching in male, but not female, VPA-derived cortical neurons. CannA or CannB treatment also normalized elevations in neuronal activity in the VPA cultures with sex-dependent effects. Preliminary in vivo findings from adolescent male and female VPA rats exposed to acute CannB administration (0.2 mg/kg i.p.) showed improved sociality in both sexes. CONCLUSIONS: These preclinical findings identify key sex differences in behaviour, and neuronal structure and function, upon exposure to VPA with more pronounced effects in female rats. Overall, these findings suggest that sex differences in the VPA model may have relevance to the sex-specific symptoms observed in ASD. This work also highlights the critical need for employing both sexes when utilizing animal models in the study of ASD if we are to improve their translational validity.

PS09.03: Molecular logic of circuit organization by autism-associated synaptic adhesion proteins

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In this presentation, recent research on the involvement of synapse-organizing proteins associated with autism spectrum disorder (ASD) will be highlighted. The focus will be on their contribution to the precise development and functioning of synapses, with a particular emphasis on the cooperative activity of these organizers in specifying synaptic connections. These insights shed light on the pathophysiology of ASD. Additionally, the presentation will explore the contextual nature of synapse organizers, whose functions differ according to the brain region or developmental stage. Lastly, the emerging role of synapse organizers in mediating synaptic plasticity will be discussed, which offers new avenues for understanding the neural mechanisms underlying learning and memory.

PS09.04: Autism-related mutations in EEF1A2 alter translation and actin bundling

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BACKGROUND AND AIM: Neurons express a unique elongation factor isoform, Eukaryotic Elongation Factor 1α 2 (EEF1A2) which replaces the ubiquitously expressed isoform Eukaryotic Elongation Factor 1α 1 (EEF1A1) as neurons develop. De novo mutations in EEF1A2 have been found in patients with severe epilepsy, autism, and intellectual disability. Our aim was to examine three of the most common mutations in EEF1A2 (G70S, E122K, D252H) found in patients with severe autism and epilepsy and determine how they impact neuronal function and translation. METHODS: We expressed the G70S, E122K, and D252H EEF1A2 mutations in HEK293 cells and mouse cortical neurons and determined their impact on neuronal function. RESULTS: We found that the the autism-associated mutations in EEF1A2 disrupt protein synthesis by slowing elongation rates. We also found that these mutations increase tRNA binding, reduce the complexity of dendritic morphology, and impair acting bundling activity. CONCLUSIONS: We found the three most common autism-associated mutations in EEF1A2 impair translation elongation and hypothesized that this is due to a broad sequestration of all tRNAs that reduces tRNA availability. We also demonstrated that the EEF1A2 mutations results in a reduction in actin bundling activity, which we posit alters neuronal morphology and activity.

Parallel Symposium 10: Cannabinoids, endocannabinoids and microglia

PS10.01: The impact of prenatal delta-9-tetrahydrocannabinol on the brain and behaviour development across the lifespan

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BACKROUND AND AIM: Up to 10% of expecting mothers use cannabis without realizing they are pregnant or to counteract effects of morning sickness. The impact of prenatal exposure to the

psychoactive delta-9-tetrahydrocannabinol (THC) on brain development and behavior from earliest stages of life to adulthood due to gestational THC-exposure is poorly characterized. To address this gap, we used magnetic resonance imaging (MRI) to examine the impact of early gestation THC during fetal brain development all the way to adulthood. In doing so, we have been able to reconstruct a timeline of how prenatal THC exposure impacts brain and behaviour across several critical developmental periods. METHODS: We will describe three specific experiments where pregnant dams were injected with vehicle or 5 mg/kg THC daily from gestational day (GD) 3-10 as means of mimicking a dosage that is roughly equivalent to a single human joint taken per day. In the first, we use an ultra-high resolution MRI paradigm to examine the brain anatomy of harvested embryos (GD 17). In the second, we examine brain development at the earliest stages of life using a dense sampling strategy from postnatal days (PND) 3, 5, 7, and 10. We further examine how brain development trajectories are related to ultrasonic vocalizations (a cry for maternal care) acquired on PND 12 after separating pups from dams and littermates. In the third, we examined brain development after weaning across childhood (PND 25), adolescence (PND 35), early adulthood (PND 60), and adulthood (PND 90). In this final experiment we further examined the relationship between these brain development trajectories with anxiety-like behavior (open field test and prepulse inhibition). RESULTS: Overall, we demonstrate that by using these detailed approaches, we can elucidate a temporal mapping of the coupling between brain and behavioural development and the deviations from a normative trajectory related to prenatal THC exposure. CONCLUSION: Given the recent legalization of cannabis and related products, experimental designs that take the entire lifespan into account will be crucial to identifying potential THC-mediated neurobiological variation.

PS10.02: Effect of acute vapourized cannabis on microglia

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BACKGROUND AND AIM: Microglia, the brain's resident immune cells, are increasingly becoming recognized for their physiological roles as well as their immunological ones. Microglia possess cannabinoid receptors and respond to cannabinoids, such as phytocannabinoids in cannabis. Administration of the primary phytocannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), typically leads to anti-inflammatory responses, but this is dependent on the route of administration (i.e., typically injection or ex vivo), duration and compounds delivered. Our goal is to understand how another relevant route of administration, inhalation, affects microglia physiological functions. METHODS: Whole cannabis plant was administered to adult, male, C57BL/6J mice for 15 min (one 15 second puff every 5 min; 3 puffs total; 0.15 g flower/puff). Four groups were utilized, mice that received control air vapour, and mice that were exposed to either: high CBD/low THC, high THC/low CBD, or balanced THC/CBD cannabis strains. Brains were isolated 30 min post-cannabis administration onset, when THC levels peak in the brain. We stained the tissue with antibodies against IBA1 (microglia and macrophages) and TMEM119 (more specific for microglia). We looked at IBA1 cell density, nearest neighbour distance and spacing index (changes in number and distribution), in regions important for cognition, memory, and emotional regulation, specifically focusing on the prefrontal cortex. We also

investigated IBA1 and TMEM119 colocalization, as well as IBA1 cell morphology. RESULTS: Microglia distribution and spacing, as ascertained by nearest neighbour distance, was altered in the prefrontal cortex of male mice. Specifically, IBA1 cells in the infralimbic area, but not the prelimbic cortex, were potentially altered in CBD containing strains versus others. In the prelimbic cortex, all IBA1 cells analyzed were colocalized with TMEM119, indicating these cells were likely all resident microglia. Furthermore, in the prelimbic cortex, although there were no changes in microglia density or distribution, microglia morphology was altered. In the balanced strain exposed group compared to control air exposed group, microglia fractal dimension was reduced, indicating a less complex morphology; and microglia lacunarity was increased, indicating altered shape. CONCLUSIONS: Our preliminary data indicates that acute cannabis exposure alters microglia morphology in the prelimbic cortex. We will use scanning electron microscopy to investigate potential changes in microglial organelles and interactions with parenchymal elements. This work will lay the foundation for understanding how vaporized cannabis exposure alters microglial form and function, and determining how these parameters change with chronic exposure and in response to stress, infection or disease. We are also investigating potential sex differences in the response of microglia to acute cannabis exposure.

PS10.03: Central actions of cannabis in neuropathic pain

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BACKGROUND AND AIM: Chronic pain is a defining feature of many diseases and a leading cause of disability for one in five Canadians. Neuropathic pain is among the most debilitating chronic pain conditions, and it is difficult to treat. To control pain, some people resort to cannabis. Pain is the most common reason for medical cannabis use, yet the evidence for its effectiveness is not well established. METHODS: In this study, we examined the behavioural and cellular effects of vapourized cannabis in a spared nerve injury model of neuropathic pain. We ask whether cannabis alleviates mechanical allodynia, a major symptom of neuropathic pain whereby innocuous stimuli such as gentle touch, elicits pain. Pulmonary route of cannabis intake is the most common method of cannabis use in people, including those who report using cannabis for pain. Vapourization of cannabis is advantageous over edibles because we can more precisely control delivery and resulting pharmacokinetics. In adult male and female Sprague Dawley rats, cannabis or polyethylene glycol (PEG) vehicle was administered by controlled vapour delivery and mechanical pain threshold assessed using the von Frey filament test. RESULTS: In male rats with established neuropathic pain, vapourized tetrahydrocannabinol (THC, 10%), THC/cannabidiol (CBD, 10%) mixture, or whole cannabis extract transiently alleviated mechanical allodynia. In female rats, treatment with these compounds also transiently reversed mechanical allodynia but to a lesser extent than in males. Furthermore, we found that whole cannabis exposure prevented the nerve injury-induced upregulation of CD11b and CD68 expressing cells (e.g. microglia) within the spinal dorsal horn, a key area for pain processing. CONCLUSIONS: Our findings suggest that vapourized cannabis extract or its constituents (THC, CBD) acutely alleviates nerve injury induced mechanical allodynia, possibly by reducing spinal microglia reactivity.

PS10.04: Role of microglial CB2 receptors in the locomotor effects of cocaine

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BACKGROUND AND AIM: Cocaine is a psychomotor stimulant with significant liability for miss use that can lead to psychological dependence. Unfortunately, there are no pharmacological approaches to the treatment of cocaine dependence and overdose death rates in the US have increased, particularly since the pandemic. Work from other laboratories found that the CB2 receptor agonist, JWH133, reduced multiple pharmacological effects of cocaine in rodents, including reduced locomotor activity, drug self-administration and the development of sensitization (i.e. increased effects following multiple treatments). Given that the primary cell type that expresses the CB2R in brain is the microglial cell, we tested the hypothesis that loss of CB2R in microglia would eliminate the effect of JWH133 and would increase cocaine locomotor effects. METHODS: Male and female mice with selective deletion of CB2R were established by breeding CB2R floxed mice with mice expressing cre under a CX3CR1 promotor. Controls included WT, global CB2R deleted mice and mice expressing the cre construct. Mice were treated with the CB2R agonist, JWH133, followed by cocaine and locomotor activity was determined in an open field. RESULTS: We discovered that CB2R signaling in microglia has sex-specific effects on cocaine behavioral responses and that it is likely that another pool of CB2R, perhaps on neurons, contributes to the overall interactions between CB2R and cocaine. CONCLUSIONS: We hypothesize the cocaine, which can activate TLR4 signaling in microglia, activates microglia and that this contributes to the behavioral effects of cocaine, perhaps by potentiating the effects of dopamine. We hypothesize further that CB2R on microglia oppose the TLR4-mediated activation and thereby dampen the effects of cocaine. Supported by NIH grant DA041212 and the Kubly Fund for Depression Research.

Parallel Symposium 11: Cerebellar wiring and vulnerability in health and disease

PS11.01: Regulation of inhibitory interneuron wiring in the cerebellum by an atypical Cadherin

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As in all brain regions, the formation of functional circuits in the cerebellum requires the precise wiring of GABAergic interneurons. Within the cerebellar cortex, interneuron populations are functionally diverse and provide specific forms of synaptic inhibition to shape information processing within the cerebellum. Interestingly, the suite of cerebellar interneurons is born from a common progenitor pool, and populates the input and output layers sequentially and according to birth order. Recent studies by our lab and others have begun to trace interneuron diversification and wiring based on their lineage, morphological, and molecular signatures. In this talk, I will present our recent efforts to identify molecular regulators of interneuron-type specific wiring using transcriptomic approaches. I will present our findings that indicate a novel role for an atypical Cadherin in mediating synapse specificity to interneuron targets within the input granule cell layer. We find that Cadherin 23 is uniquely expressed by

mossy fiber (MF)-forming neurons and their inhibitory Golgi cell target, but not in their excitatory target cells. To test the hypothesis that Cadherin 23 is a regulator or MF-Golgi cell synapse specificity, we performed a series of gain-of-function and loss-of-function experiments. Cadherin 23 is a sensory cadherin essential for sensory transduction, with human mutations causing deafness and blindness in Usher's Syndrome. However, its role in the CNS is unexplored. Together, our findings highlight a novel role for Cadherin 23 for synapse formation within the brain, and for inhibitory versus excitatory target specificity within the cerebellum.

PS11.02: Fundamental mechanism in interneuron synaptic organization and function

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BACKGROUND AND AIM: The cerebellum is an essential brain structure that functions to generate coordinated movement and is important for motor learning. Developmental and degenerative disorders that affect the cerebellum have dramatic effects on stance, balance, and gait. Despite this we still have limited understanding of how the cerebellum develops to establish functional connections. Nitric oxide (NO) is an important signaling molecule found highly expressed in cerebellar inhibitory interneuron function. NOS1, the enzyme that generates NO is highly expressed in the cerebellum and NOS1 deficiency results in profound defects in gait including ataxia. To better understand how NOS1 is regulated we focused on the role of a scaffolding protein that directly couples to NOS1 - NOS1 adaptor protein (NOS1AP). NOS1AP has been shown to play an important role in the synapse and disease states including bipolar disorder and schizophrenia. In addition, we have shown an important role that NOS1AP plays in the development and maintenance of synaptic morphology through the regulation of members of the RhoGTPase family of proteins. How NOS1AP functions with NOS1 in cerebellar systems remains unknown. METHODS: To better understand the role of NOS1AP in the development of the CNS, we generated a NOS1AP mutant mouse and performed a battery of behavioural assessments including motor function, learning and memory, fear conditioning trials and anxiety. As well, morphological, and histochemical analysis combined with electrophysiology were utilized to assess synaptic function in these mutant mice. RESULTS: We have identified that several unique NOS1AP isoforms are expressed in different cell types within the developing cerebellum. This includes an isoform we have identified as NOS1APa. Mice lacking the NOS1APa isoform have gait defects, consistent with cerebellar dysfunction. Consistent with this we find that NOS1APa is restricted to molecular layer interneurons and plays an important role in maintaining NOS1 within the dendrites and synapses of molecular layer interneurons. In addition, NOS1APa mutant mice have alterations in the firing frequency of Purkinje cell synapses. Similar phenotypes are seen in a conditional mutant mouse, where NOS1APa is specifically deleted only in MLINs. CONCLUSION: These findings point to the importance of NOS1AP isoforms in cerebellar development with the NOS1APa isoform functioning to restrict NOS1 and NO to dendrites and synapses of molecular layer interneurons which is necessary for the regulation of complex motor behaviours.

PS11.03: Modulation of microglia responses to prevent cerebellar injury and function

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Each year nearly 2% of infants are born very preterm (VPT) (<32 weeks of gestation). Despite advances in perinatal care, a dramatic improvement of their survival rates and a major decrease in severe brain injury, long-term neurodevelopmental deficits remain a significant burden affecting nearly 50% of VPT. Cerebellar underdevelopment and cerebellar injury (CBI) are increasingly recognized findings in VPT children with alterations of higher-order functions such as learning, communication and social skills. While the cerebellum was long known to regulate coordination and motor behaviors, evidence now show that altered cerebellar development can modulate higher cerebral development and complex functions. The pathophysiological mechanisms underlying cerebellar injury, underdevelopment and intrinsic repair capacity are still poorly understood preventing development of targeted interventions. To detail these understudied mechanisms involved in cerebellar underdevelopment, we are using our translational model of CBI combining the most frequent direct insult, cerebellar hemorrhage with inflammation in the immature neonatal (P2) mouse brain. This model is unique and mimics multiple aspects of the human condition. Thus, as observed in clinical settings, our model translates the early and massive innate immune response of microglial cells within cerebellar tissue associated to cerebellar underdevelopment and long-term motor and socio-cognitive deficits in mice. Using a selective transgenic tool for microglia depletion, mice with reduced microgliosis and exposed to cerebellar perinatal insults showed preserved cerebellar growth and improved behavioral deficits. Characterization of microglia tissue repair responses showed persistent alterations of cellular proliferation and tissue remodeling state two weeks after injury along with decreased microglia phagocytosis capacity and alterations of inhibitory and excitatory inputs onto Purkinje cells. By starting to unravel the role of microglia in cerebellar injuries, cerebellar underdevelopment and the detrimental impact of these injuries on global functional outcomes, we will fill an important knowledge gap on perinatal brain injury affecting preterm newborns. This knowledge should pave the way for development of novel neuroprotective therapies that are critically needed to protect the premature brains from injury and prevent long-term developmental consequences of cerebellar underdevelopment.

PS11.04: Investigation of cerebellar pathology in MATR3 S85C knock-in mouse model of ALS

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that leads to fast disease progression as patients die within 2-5 years after disease onset. Clinical symptoms of ALS patients include motor function impairment, muscle weakness and paralysis. The key neuropathological feature of ALS is motor neuron degeneration; therefore, most ALS studies have been focused on motor neurons for more than one hundred years since Charcot's discovery. Recently, clinical studies from ALS patients have provided evidence that cerebellar atrophy and Purkinje cell degeneration is also associated with ALS. Little is known how cerebellar pathology contributes to the disease process and how Purkinje cells undergo death. My lab established a new ALS mouse model, MATR3 S85C knock-in (KI) mice. A missense mutation

S85C is the most frequently identified ALS-linked mutation in MATR3, which encodes an RNA binding protein involved in RNA splicing. The KI mice recapitulate key behavioral and neuropathological features of ALS including motor deficits, neuromuscular junction (NMJ) defects and cerebellar pathology associated with Purkinje cell loss and neuroinflammation. This knock-in model closely mimics the human disease genotype and follows a natural disease course, allowing examination of the consequence of a single pathogenic mutation (i.e. the S85C missense mutation) and dissection of the early disease process. Using this model, we are trying to answer the following questions: 1) how do Purkinje cells die? 2) what is the disease-initiating event that trigger degeneration? and 3) does inflammatory response by the brain's innate immune system, i.e. microglia, protect Purkinje cells from dying or accelerate the dying process? Our studies will uncover early disease events and mechanisms of degeneration in Purkinje cells, and reveal the role of microglia in the disease process particularly during early stage ALS. Defining the key early events will facilitate the development of early prevention and intervention strategies for ALS.

Parallel Symposium 12: Brain wide network mapping in mice and its applications

PS12.01: Wide field single photon cortical imaging in combination with sub-cortical or cerebellar neuropixel or fiber photometry provides point source activity measures in the context of larger cortical networks

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Understanding the basis of brain function requires knowledge of cortical operations over wide spatial scales and the quantitative analysis of brain activity in well-defined brain regions. Matching an anatomical atlas to brain functional data requires substantial labor and expertise. Here, we developed an automated machine learning-based registration and segmentation approach for quantitative analysis of mouse mesoscale cortical images termed Mesonet. Such tools are ideal for developing an understanding of long-range functional relationships. For example the cerebellum is involved in not only motor tasks, but also a wide range of cognitive functions. Where and how the cerebellum receives or outputs these diverse streams of information to perform complex processing remains unclear. We study functional connectivity between the cerebellum and the dorsal cortex of the mouse brain using Neuropixel probes to record spiking activity of individual cerebellar neurons and mesoscale Ca2 imaging to assess population activity of the entire dorsal cortex. We show that cerebellar neurons were dynamically coupled with diverse cortical networks including the retrosplenial and visual networks, two systems not commonly associated with cerebellar function. Subcortical areas can be assessed using chronic recording strategies using tetrode recording (termed mesotrode) or fiber photometry (mesofiber) and provide a means of relating spiking within specific nuclei or even peripheral nerves to wide-scale patterns of cortical activation. These findings demonstrate that different combinations of cortical-subcortical networks generate multi-scale network activity, offering new insights into the neural mechanisms underlying specific behaviors. While cortical mesoscale imaging uses wide-field microscopy, the lab is also employing mesoscale cellular 2-photon imaging and can identify ensembles of neurons across large spatial distances including transcallosal connections.

PS12.02: Identification of specific cerebral networks functionally altered during neuropathic pain in awake mice, using ultrafast ultrasound imaging

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BACKGROUND: Chronic pain is due to abnormal, maladaptive neuronal plasticity in the structures known to be involved in pain perception. Our hypothesis is that the aforementioned maladaptive plasticity in these brain areas could be key mechanisms for the development of comorbidities, such as anxiety and depression. Functional ultrasound (fUS) imaging is a sensitive and versatile neuroimaging modality, able to quantify with a large field of view (indirectly) neuronal activation and measure functional connectivity (FC), an indirect measure of the functionality and strength of brain networks. AIM: This study aimed at identifying, using fUS imaging, how the functionality of brain networks is changing in link with neuropathic pain and the comorbidity associated to it. METHODS: Using fUS imaging, we measured the functional connectivity (FC) at rest in awake, head fixed animals, subjected to neuropathic pain (2W cuffing of the sciatic nerve), or anxiety (8W) or depression (12W). Behavioural tests were carried out to follow the various symptoms. RESULTS: Our results show time-specific alterations of the networks. At the emergence of neuropathic pain, FC within regions involved in the sensory aspect of pain are altered and then gradually mutating overtime (8W-12w) into some changes in areas involved in the emotional aspect of pain, such as the anterior part of the cingulate cortex and the Insular cortex. Our study also demonstrates changes of functional connectivity in sham operated animals compared with naïve animals, suggesting that postoperative pain induces functional changes in some brain networks. CONCLUSION: Various brain areas of the 'pain matrix' undergo plastic changes during with the various stages of the disease and the associated comorbidities

PS12.03: Memory networks in mice

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Memory formation and consolidation are believed to engage a complex network of brain regions that evolve with the age of a memory trace. The study of these networks can inform us of hub regions that are essential in the different steps of memory consolidation, together with the analysis of differences in functional connectivity between brain areas. In this study, we unraveled new circuits involving the hippocampus, the thalamus, and the neocortex that are recruited to recall remotely acquired fear memories. Moreover, we identified the single-cell contribution of thalamic regions and their different recruitment in developing memories that become generalized over time. In particular, we studied the anterodorsal nucleus (ADn) and the laterodorsal nucleus (LDn) of the thalamus, 2 regions containing head direction cells. While they are equally engaged to form a proper representation of the space during fear memory acquisition, at a remote time point their recruitment diverges: while the ADn is silenced, the LDn becomes a hub region of the memory network. In this work, using a miniaturized microscope to study the activity of single cells over time, we are correlating their neuronal activity with the behavior of

the mice while acquiring and remembering contextual fear memories. Thalamic head direction cells are identified and their contribution to spatial representation related to fear memory is studied.

PS12.04: Disruption of white matter maturation and its impact on brain-wide networks and behaviour

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BACKGROUND: White matter tracts provide a scaffold for network-wide interactions in the brain. White matter maturation continues throughout childhood and adolescence with ongoing myelination and increases in axon calibre that result in more densely packed tracts. Disruptors of white matter in childhood likely alter the trajectory of brain development with consequences for network communication and behaviour. AIM: This research aims to describe the impact of disruptors of white matter in development on microstructural and brain-wide trajectories of maturation and its behavioural consequences. METHODS: White matter is vulnerable to mild traumatic brain injury. Influences of mild traumatic brain injury on brain-wide white matter microstructure are described in children and juvenile mice with multicompartmental modelling of diffusion MRI, complemented by immunohistochemistry and electron microscopy in mice. Behaviour in children is assessed with the Child Behavior Checklist and in mice with the elevated O maze. RESULTS: Brain-wide white matter density and global network measures of segregation are altered in children that experienced a mild traumatic brain injury early in life. Assessment of brain microstructure before and after injury indicates that the trajectory of white matter maturation is changed by mild traumatic brain injury and deviation from the typical maturational trajectory predicts anxiety behaviours in females specifically. Our juvenile mouse model of mild traumatic brain injury also results in anxiety-like behaviours and is accompanied by indicators of enhanced myelination in late-maturing white matter tracts such as the corpus callosum. CONCLUSIONS: Evidence from both children and juvenile mice demonstrate that disruption of white matter alters the trajectory of white matter maturation and contributes to changes in network-wide structure and anxiety. The impact on white matter maturation is dependent on the maturation stage of the white matter at the time of disruption.

POSTER SESSIONS

Poster Themes

A - Development
B - Neural Excitability, Synapses, and Glia: Cellular Mechanisms
C - Disorders of the Nervous System
D - Sensory and Motor Systems
E - Homeostatic and Neuroendocrine Systems
F - Cognition and Behavior
G - Novel Methods and Technology Development
H - History, Teaching , Public Awareness and Societal Impacts in Neuroscience

POSTER SESSION 1

P1-A-1: Maternal exposure to prostaglandin e2 affects hippocampal electrophysiology in mice offspring - a link to autism spectrum disorders.

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Prostaglandin E2 (PGE2) is a lipid signaling molecule involved in early healthy brain development. Exposure to environmental risk factors such as air pollutants, infections, inflammation or drugs such as acetaminophen during early pregnancy impact PGE2 levels and have all been linked to Autism Spectrum Disorders (ASDs). Our previous studies show that maternal exposure to PGE2 and the lack of the PGE2 producing enzyme Cyclooxygenase-2 (COX2) results in sex-specific abnormal dendritic arborization, cell soma size, branch length, and looping within the cerebellum and ASD-like behaviors including motor deficits and anxiety in mice offspring. In this study, we investigate sex-dependent effects of prenatal PGE2 exposure on hippocampal electrophysiology in the C57bl/6 mice offspring at postnatal day 90-100. We measured long-term potentiation (LTP), paired-pulse facilitation (PPF) and input/output (I/O) responses and the expression of glutamate receptor components NMDA subunit 2A (GluN2A), AMPA subunit GluR1 and beta-actin. We found that PGE2 exposure decreased LTP in males and I/O responses in females at higher stimulation intensities with no effect on PPF. PGE2 also increased the expression of GluN2A in males with no effect on GluR1 or beta-actin. Overall, our data suggests that prenatal PGE2 exposure disrupts innate sex differences by reducing LTP maintenance in males, while impairing basal synaptic transmission in females. Interestingly, upregulated expression of GluN2A observed in PGE2 males may reflect a homeostatic compensatory response to impaired synaptic plasticity, suggesting that in utero exposure to PGE2 shifts both physiological responses to neural activity, and the complement of NMDARs required for learning and memory which are functions implicated in ASD.

P1-A-2: Development and neural stem cell dynamics of the zebrafish rostral migratory stream

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Cellular migration is a fundamental mechanism for brain development, function and potential recovery after injury. The rostral migratory stream (RMS) is characterized by the continuous migration of neuroblasts from neural stem cells (NSCs) of the forebrain to the olfactory bulbs (OB), where they differentiate into neurons. The RMS was first described in mammals, though less is known in the highly neurogenic zebrafish model where a similar RMS-like structure persists. At present, we lack knowledge regarding the formation and behavior of the RMS as a distinct migratory route from larval to adult life stages, and how the RMS shapes OB populations of neurons. To characterize the development of the zebrafish RMS, I investigated the production and migration of newborn cells from the forebrain to the bulbs across larval, juvenile and adult stages. A double-labelling strategy using proliferative markers was employed to track the progression of newborn cells from the origin of the RMS toward the OB. Maturation of progenitors into functional neurons was characterized using neuronal-specific markers. My results suggest a clear change in NSC proliferative behavior, and highlight the progressive formation of the RMS, commencing between larval and juvenile stages. Over this same developmental window, the RMS contributes to first exclusively populating the OB with GABAergic neurons, and later adding dopaminergic neurons between juvenile to adult stages. This study will offer novel insight towards lifelong RMS-driven NSC activity, serving as a stepping stone to next study RMS modulation.

P1-A-3: Developmental cognitive neuroimaging and poverty: a preliminary global research synthesis

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The purpose of this global meta-analysis aimed to assess: 1) whether the effects of family poverty or low SES on cognition as reflected by neuroimaging results are consistently found to be detrimental; 2) the strength of the effect sizes (ES). The preliminary literature search on main databases (WEB of SCIENCE; PUBMED; MEDLINE: PSYCNET; GOOGLE SCHOLAR; SCIENCEDIRECT) included 52 experimental studies and intervention studies from 1988 to 2017. Only 8 (13%) were from middle or developing countries; most of the studies (87%) were conducted in Western countries. We found no associations between the ES' or their significance of data and major recognized global indices of income or socioeconomic inequality status of the country (using sources such as UN, The World Bank, IMF and OECD). Least squares Bayesian ANOVA models, weighted by sample sizes, revealed very strong evidence that the estimated ESs were statistically heterogenous across countries. A mix of Bayesian and standard hypothesis testing sets of analyses all converged to indicate unequivocally that, despite the heterogeneity across studies, high and low SES groups performed similarly in most of the behavioral tasks concurrent with neuroimaging. Except for combined fMRI+sMRI studies, which yielded very large ESs, the effects were generally small to intermediate with rather modest reliability in the findings. The strongest ESs for differences between high and low SES were found in relation to mathematical performance, language and socioemotional processes, closely followed by intermediate effects concerning attention and working memory. We suggest these results are best understood in relation to global structural or environmental set of ecological factors beyond the individual children and their families.

P1-A-4: Characterization of steroidogenic enzymes in the embryonic brain and placenta in mice

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Hormones play a fundamental role in driving neural sex differences in the developing brain, with the secretion of testosterone from male gonads around birth thought to drive brain masculinization. Unexpectedly, we recently discovered evidence that sex dimorphism in the hypothalamus might began prior to gonadal differentiation, with vasopressin+ neurons displaying sex dimorphism by E13.5. Given that the gonads are still differentiating at this time point, we hypothesized that local steroidogenesis might influence embryonic neural sex differentiation. In addition to the brain, the placenta is also a highly steroidogenic organ, which notably, also has a biological sex matching that of the fetus. Here, we examined if key enzymes in the steroidogenic pathway were expressed in the placenta and/or hypothalamus during early embryogenesis. Specifically, we focused on STAR, responsible for transporting cholesterol into the mitochondrial to initiate steroidogenesis, and CYP11a1, which catalyzes the first step in the steroidogenic pathway. We used qPCR and RNAScope in placenta and hypothalamus to quantitate and spatially visualize these transcripts, respectively. Our preliminary data at E11.5 in mice show the presence of both STAR and CYP11a1 in the placenta and hypothalamus, with transcripts higher in males than in females. Ongoing studies are characterizing the expression of these enzymes in regions outside the hypothalamus, as well as across embryonic developmental time points. With growing evidence showing sex differences in neurodevelopmental disorders such as Autism Spectrum Disorders, understanding the interaction of the brain and placenta in driving early sex differences may provide clues to deciphering how these disorders emerge in a sex-specific manner.

P1-A-5: Extracellular vesicles and synthetic nanoparticles (PLA-PEG) loaded with donepezil for a better treatment of Alzheimer's disease

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Donepezil (DNZ) is one of the approved drugs for Alzheimer's disease (AD). However, DNZ exhibits low bioavailability. In this context, nanoparticles of Poly (lactic acid) with PEG (PLA-PEG) proved to be an effective way to prolong the circulating half-life but its applications remain limited due to its immunogenicity. On the other hand, extracellular vesicles (EVs), released by all body cells, may have longer circulation half-lives. We hypothesize that better drug bioavailability and efficacy will be achieved with EVs loaded-DNZ than synthetic PLA-PEG nanoparticles (NPs)-loaded DNZ. For this, human plasma derived-EVs (pEVs) were enriched and PLA-PEG NPs were synthesized by nanoprecipitation. The polydispersity index was 0.3 ± 0.01 and 0.1 ± 0.02, the diameter size 126 ± 0.38 nm and 107 ± 0.15 nm, and the zeta potential -42 ± 1.52 mV and -44 ± 0.50 mV for pEVs and PLA-PEG NPs, respectively. DNZ encapsulation efficiency was 58 ± 1.45% for pEVs-DNZ and 48 ± 0.92% for PLA-PEG-DNZ. No toxicity and morphological changes was observed on Danio rerio zebrafish. After six days of treatment, hyperactivity was observed in PLA-PEG-DNZ and free DNZ groups but not in EVs-DNZ group. Interestingly, the inhibition of the enzyme acetylcholinesterase activity in the fish head was higher with the pEVs-DNZ

than with PLA-PEG-DNZ or the free drug. The biodistribution analysis showed that pEVs labelled with the fluorescent probe PKH26 was present in the brain parenchyma, while PLA-PEG-Cy5 remains mostly within the bloodstream. Overall, DNZ loaded-pEVs offer higher brain targeting of the drug.

P1-A-6: Investigating the mechanism of programmed cell death of hippocampal Cajal-Retzius cells

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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. We will also use viral-mediated gene delivery to overexpress proteins involved in cell death in order to monitor the progression of CR cell death to elucidate the mechanism of CR cell death in the postnatal hippocampus. 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-7: In vivo functional study of an alternative protein encoded by the gene ZYX/zyx-1 with implications for synaptic development and dystrophinopathies

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Defective synapse maintenance and muscle degeneration are involved in Duchenne muscular dystrophy, which is caused by a deficiency in the sarcolemmal protein dystrophin. The gene ZYX encodes Zyxin, a cell adhesion and mechanosensation protein, and its C. elegans homolog, zyx-1, is required for synapse development and dystrophin-dependent muscle degeneration. Indeed, either overexpression or deficiency of zyx-1 ameliorates the muscle degeneration phenotype caused by dystrophin deficiency. In addition to encoding the canonical protein Zyxin, the gene ZYX/zyx-1 codes for a second distinct protein named AltZyxin produced from an alternative open reading frame (altORF), as revealed by mass spectrometry studies in both humans and C. elegans. AltORFs-encoded proteins have been found to physically interact with the canonical protein encoded by the same gene, and to modulate their cellular localization and molecular function. To decipher the mechanism by which the gene ZYX/zyx-1 regulates synapse maintenance and muscular degeneration, we are investigating the function of the alternative

protein AltZyxin in synapse and muscle biology in C. elegans. For this, we generated CRISPR-engineered targeted mutations to disrupt either of the two encoded proteins specifically, and determine the synaptic, muscle, and behavioural consequences. Neuron- and muscle-specific rescue assays and localization studies with fluorescent reporters will inform on the functions and interplay between Zyxin and AltZyxin. Finally, in vivo TurboID screening is being prepared to identify AltZyxin interactors.

P1-A-8: The extracellular matrix protein MIG-6/papilin mediates the maintenance of neuronal architecture

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After the embryonic assembly of the nervous system, neuronal circuits need to persist lifelong, but how neuronal organization is protected throughout life is not well understood. We demonstrated that cell-specific molecular mechanisms maintain neuronal architecture. In cell-adhesion molecule mutants sax-7/L1, neuronal structures develop normally but later become disorganized. Through a genetic screen, we uncovered that loss of the extracellular protein MIG-6/Papilin suppresses sax-7 neuronal defects. MIG-6/Papilin harbors a papilin cassette domain, present also in the extracellular matrix remodeling enzyme ADAMTS, which we show is required for neuronal maintenance. Further, mig-6 short isoform functions post-developmentally from muscle to non-autonomously impact neuronal maintenance, in a mig-17/ADAMTS-dependent manner. Loss of mig-6 leads to the accumulation of extracellular collagen IV. Collagen IV levels and crosslinking state are required for the suppression of sax-7/L1 neuronal defects by mig-6/Papilin mutation, as the post-developmental depletion of collagen IV, or of its crosslinking enzyme peroxidasin, reinstates neuronal maintenance defects in sax-7; mig-6 mutants. Notably, loss of mig-6 bestows enhanced protection of neuronal organization in conditions of increased body movements enabling neuronal architecture to endure lifelong stress. Understanding general principles of neuronal maintenance, which involve the regulation/remodeling of the extracellular matrix, will provide insights into the pathogenic mechanisms of understudied neurodegenerative conditions.

P1-A-9: Extracellular matrix and the long-term maintenance of neuronal architecture

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After the initial assembly of the nervous system during embryogenesis, neuronal circuits need to persist lifelong in the face of maturation, growth, body movements, and aging to ensure its functions. The mechanisms dedicated to ensuring the long-term maintenance of neuronal architecture remain poorly understood. Research in our lab, using the model organism Caenorhabditis elegans, has uncovered neuronal and extracellular matrix molecules that are central to neuronal maintenance and act with great cellular specificity. One molecule identified in our genetic screen is MIG-6/Papilin, a conserved ADAMTS-like extracellular matrix protein, whose mutations suppress neuronal maintenance defects in mutants for sax-7/L1CAM cell adhesion molecule, and help maintain neuronal organization under conditions of increased mechanical stress. At the level of the extracellular matrix, mig-6 mutants display fibrotic accumulations of collagen IV, whose high levels and reticulation are both necessary for neuronal maintenance. We hypothesize that the extracellular matrix is dynamically regulated to respond to the demands of maintaining neuronal organization, and that a crosstalk between neurons and the extracellular matrix is part of the mechanism. We are currently systematically addressing the contribution of key extracellular components and regulators in neuronal maintenance. A better understanding of the molecular mechanisms involved in the maintenance of neuronal architecture and connectivity may help identify key factors influencing the onset and progression of neurodegenerative conditions.

P1-A-10: Deciphering the role of Syndecan in regulating the number of cellular projections in neurons and other polarized cells

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Disturbances in cell morphology are intrinsically associated with defects in cell functions. Proper morphogenesis is crucial for the development of highly specialized cells like neurons. Important progress has been made in deciphering the morphologic processes of outgrowth and guidance of cellular projections, but the regulation of the number of neurites or of cellular projections stemming from the cell body are largely unknown. Studies conducted by our group in Caenorhabditis elegans have revealed that the conserved heparan sulfate proteoglycan SDN-1/Syndecan is a key player in regulating cell-autonomously the number of cell projections in the excretory canal cell, a model for morphogenesis study, which shares developmental mechanisms with neurons. Our findings show that the guidance molecule UNC-6/Netrin, its main receptors UNC-40/DCC and UNC-5/UNC5, as well as the extracellular membrane receptor integrin, are implicated in the Syndecan-mediated control of cell extension number. We are progressing towards testing whether the precise localization and dynamics of these molecular players depend on the function of Syndecan. Furthermore, we will screen for intracellular interactors of Syndecan using a TurboID approach and finally assess whether the same mechanism is at play in

developing neurons. We expect that these studies will contribute to the discovery of fundamental principles of nervous system development and function.

P1-A-11: The Cell Adhesion Molecule Sdk1 Shapes Assembly of A Retinal Circuit That Detects Localized Edges

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In the mouse retina, nearly 50 different retinal ganglion cell (RGC) types sample the visual scene for distinct features such as contrast, motion, or orientation. This feature selectivity arises from the synapses between each RGC and specific subsets of interneuron types in the retina. How the dendrites of these cells arborize and coalesce into functional circuits remains poorly understood. Here, we examined the hypothesis that RGCs employ molecular recognition systems to meet this challenge. By combining calcium imaging and type-specific histological stains, we define a family of circuits that express the recognition molecule Sidekick-1 (Sdk1), which include a novel RGC type (S1-RGC) that responds to local edges. Genetic and physiological studies revealed that Sdk1 loss selectively disrupts S1-RGC visual responses, which result from a loss of excitatory and inhibitory inputs as well as selective dendritic deficits on this neuron. We conclude that Sdk1 shapes dendritic growth and wiring to help S1-RGCs become feature selective.

P1-A-12: Investigating The Role of The Prefrontal Cortex in Regulating Neonatal Development of Neuronal Networks in The Claustrum

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The claustrum (CLA) is a 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 time course of circuit maturation between the PFC and the CLA remains elusive. To determine the developmental timeframe of PFC inputs to the CLA, i.e. PFC-CLA inputs, we injected anterograde neural tracers into the PFC of Ai9 transgenic mice at seven-day intervals from postnatal day (P) 1 up to P42, then assessed the number of fluorescent postsynaptic cells in the CLA 14 days post injection. We found that monosynaptic PFC-CLA connectivity does not fully develop until after P28. However, despite the low number of labeled CLA cells between P14 and P28, there was a dense presence of PFC axon terminals. This suggests protracted maturation of PFC-CLA connections that extends during puberty in mice (~P21). Of note, while excitatory neurons and somatostatin-expressing inhibitory neurons largely mature by P7 in the CLA, parvalbumin-expressing (PV+) inhibitory neurons are absent up to P14, but their number drastically increases between P21 and P28. Hence, the onset of PV expression in the CLA appears to be corollary to the establishment of PFC-CLA synapses ~P28. This may suggest that maturation of PV+ neurons in the CLA is gated by the excitatory synaptic drive of PFC inputs. Using chemogenetics, we are currently exploring whether inducing excitatory/inhibitory modulation of

CLA-projecting PFC neurons could lead to precocious/delayed PV expression in CLA inhibitory neurons, thus ultimately disrupting excitatory-inhibitory balance in the CLA during adolescence.

P1-A-13: Investigating the role of Wnt signaling during retinotectal circuit development

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The development of topographic maps in the visual system requires both genetic and sensory experience-dependent factors, but how these different mechanisms interact is poorly understood. In the retinotectal system, Wnt3A is a target-derived ligand that influences axon guidance and receptive field plasticity, suggesting that it could facilitate circuit development through both experience-dependent and experience-independent pathways. In the present study, we aimed to clarify the functional role of Wnt signaling in the developing retinotectal circuit of Xenopus laevis tadpoles. We first used a transgenic reporter line (pbin7Lef-dEGFP) for canonical Wnt signaling to confirm the presence of Wnt activity in the optic tectum during retinotopic refinement. We found that Wnt3A expression in postsynaptic tectal neurons increases miniature excitatory postsynaptic current (mEPSC) frequency, AMPA/NMDA ratios, and the density of postsynaptic puncta, indicating a role for Wnt3A in promoting synaptic maturation. Overexpression of Wnt3A in tectal neurons also increased total dendritic branch length after an 8-hour imaging period. Moreover, subjecting animals to visual stimulation, but not darkness, increased the length of dendritic branches in Wnt3A-expressing neurons relative to controls, suggesting that Wnt3A may promote dendritic branch growth through a sensory-dependent mechanism. We also investigated the influence of Wnt signaling in regulating retinal ganglion cell (RGC) axon morphology, showing that the disruption of presynaptic Wnt signaling increases the number of axon branches. Together, these results demonstrate the versatility of Wnt signaling at both sides of the synapse during retinotectal circuit development.

P1-A-14: Roles of sax-7/L1CAM in the long-term maintenance of neuronal architecture

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Whereas remarkable advances have uncovered mechanisms that drive nervous system assembly, the processes responsible for the lifelong maintenance of nervous system architecture remain poorly understood. After its initial establishment during embryogenesis, neural architecture persists throughout life in the face of growth, maturation, addition of neurons, body movements and aging of the animal. To decipher the mechanisms of maintenance of neuronal architecture, we use the model C. elegans. The protein SAX-7, which is homologous to the vertebrate L1 protein family of neural adhesion molecules, is required for maintaining the organization of neuronal ganglia and fascicles after their successful initial embryonic development. We previously generated a null allele that removes the sax-7 locus, which enabled us to show that sax-7S isoform is key in neuronal maintenance and that its post-developmental expression is sufficient to maintain neuronal organization. Interestingly, the majority of SAX-7S is cleaved in its extracellular domain, and we find that the cleaved SAX-7S fragments together, but not individually, can fully support neuronal maintenance in vivo. We are addressing the role and localization of these cleaved fragments, including by testing their function with single-copy transgenes. We are further testing the function of SAX-7S in cells neighboring neurons. Our studies on the conserved protein SAX-7/L1CAM

in long-term neuronal maintenance in the worm are expected to contribute to deciphering processes that go awry in some neurodegenerative conditions.

P1-A-15: Syndecan, netrin, guidance receptors and Rho-family GTPases cooperate to regulate the number of neurites/cellular extension in neurons and other polarized cells

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The function of neurons or other polarized cells relies on specific morphologies such as neurites or extensions. Whereas mechanisms driving axon outgrowth and guidance have been elucidated, how neurite/extension number is regulated in a developing cell remains unknown. In C. elegans mutants defective for heparan sulfate chain biosynthesis of HSPG proteoglycans, we found that unipolar neurons instead develop two neurites from the soma, and that another polarized cell, the excretory cell, develops up to 8 canals instead of 4. To elucidate mechanisms controlling cell extension number, we have first focused on the excretory cell as its defects are more penetrant and it shares common developmental mechanisms with neurons. We show that the conserved HSPG Syndecan/SDN-1 is key in this mechanism, cell-autonomously controlling cellular extension number during embryogenesis. Further, the guidance cue UNC-6/Netrin and the guidance receptors UNC-40/DCC, UNC-5/UNC5 and SAX-3/Robo, cooperate with SDN-1 to restrict the number of cellular projections. We also find that SDN-1 acts through the Rho-GTPases CED-10/Rac and MIG-2/RhoG to control cellular extension number. Our findings uncover an HSPG-regulated system ensuring the establishment of proper cell extension number during polarized cells development. Given the evolutionary conservation of the developmental mechanisms implicated, this work contributes to understanding the cellular and molecular bases of the development of precise cellular morphologies in varied cell types across animals, including neurons.

P1-A-16: Characterization of astrocyte primary cilia in the adult nervous system in health and disease

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Primary cilia are single 'hair-like' projections found on the surface of most eukaryotic cells. The primary cilia is rich in receptors and signaling molecules involved in developmental patterning and cell cycle maintenance. New roles for primary cilia are being investigated in context of brain development, function, and disease. However, the role of primary cilia in cells of the adult central nervous system (CNS) remains to be better understood. This is especially the case with primary cilia in astrocytes, a major glial cell type that plays numerous functions in CNS health and disease. Here, we conduct an in-depth analysis of the primary cilia in astrocytes in the mature cortex and hippocampus using molecular analysis and confocal imaging. Furthermore, we investigate the properties of the primary cilia in reactive astrocytes in a mouse model of Alzheimer's disease (APP/PS1 model). Our results suggest there are differences between primary cilia in astrocytes and neurons with respect to their structure and molecular composition. Moreover, there appears to be greater heterogeneity in the properties of astrocytic primary cilia that is related to brain region and astrocytic reactive state. Further experiments are planned to investigate the function of astrocytic primary cilia and to better understand their role in CNS health and disease.

P1-A-17: Repeated exposure to high-THC Cannabis smoke during gestation alters sex ratio, behavior, and amygdala gene expression of Sprague Dawley rat offspring

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Due to the recent legalization of Cannabis in many jurisdictions and increasing THC content among new Cannabis strains, there is an urgent need to understand the impact of its use during pregnancy on fetal neurodevelopment and behavior. To this end, we repeatedly exposed female Sprague-Dawley rats to Cannabis smoke (n=12; Aphria 'Mohawk'; 19.51% THC, <0.07% CBD) or room-air control (n=10) from gestational days 6 to 20. Maternal reproductive parameters, behavior of the adult offspring, and gene expression in the amygdalae of offspring were assessed. Cannabis smoke exposure did not affect body temperature in dams, but more boli were observed before and after exposure. Maternal reproductive parameters were not altered by exposure to Cannabis smoke; however, a significant increase in the male-to-female ratio was noted in the Cannabis-exposed litters. In adulthood, both male and female Cannabis smoke-exposed offspring explored the inner zone of an open field significantly less than control offspring. Gestational Cannabis smoke exposure did not affect behavior on the elevated plus maze test or social interaction test in the offspring. Cannabis-exposed offspring were better at visual pairwise discrimination and reversal learning tasks. Analysis of gene expression in the adult amygdalae revealed subtle changes in genes related to development, cellular function, and nervous system disease in a subset of the male offspring. These results demonstrate that repeated exposure to high-THC Cannabis smoke during gestation alters maternal physiological parameters, sex ratio, and anxiety-like behaviors in the offspring into adulthood.

P1-A-18: THC in adolescence dysregulates the signaling pathway that orchestrates the development of the dopaminergic system

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Exposure to tetrahydrocannabinol (THC), the main psychotropic constituent of cannabis has been steadily increasing amongst young adolescents, regardless of gender. This raises concerns as critical, neurodevelopmental processes are occurring during this age period. The prefrontal cortex (PFC), one of the last brain regions to develop, is still undergoing maturation. For instance, in mice, dopamine axons originating from neurons in the VTA are still growing to the PFC, promoting the refinement of late adolescent inhibitory control, critical in adult life. This protracted period is controlled by the guidance cue Netrin-1 and its receptor gene, DCC, whose expression in dopamine neurons is influenced by the microRNA, miR-218. Research from our lab has shown that exposure to drugs of abuse alters this guidance system, resulting in disrupted dopamine connectivity and consequences in inhibitory control. Currently, the impact of adolescent THC exposure on PFC dopamine development and adult inhibitory control remains poorly understood. To study this, male and female mice received 5 intraperitoneal

injections of vehicle or THC 5 mg/kg, once every other day from PND22. After reaching adulthood, separate cohorts underwent molecular, behavioral, and neuroanatomical analysis. Males, but not females, show alterations in expression of DCC/miR-218, accompanied by altered dopamine connectivity in the PFC and domain-specific consequences in inhibitory control. Our results suggest that THC exposure in adolescence alters adult inhibitory control in a sex- and impulsivity domain-specific manner.

P1-A-19: Characterizing the gut microbiome in autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD)

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Children with attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) often experience comorbid gastrointestinal (GI) issues and engage in selective eating behaviours which can affect gut microbial composition. Understanding the relationship of diet, gut microbial composition, and behaviour is critical in elucidating the underlying etiology in children with ADHD and ASD. The primary aim of this exploratory study is to determine whether changes in gut microbial composition are associated with an increase in reported GI symptoms and behavioural symptoms. The second aim is to explore the impact of diet intake on the gut microbiome and behaviour. Participants consisted of children ages 6-17 inclusive (n=23), with a diagnosis of ASD and/or ADHD. Each participant received a study package containing diet questionnaires, behavioural questionnaires, and stool sample collection kits. Questionnaires and stool samples were collected daily to identify changes in behaviour, diet composition and gut microbial composition across a continuous 14-day study period. The microbial community of the stool samples were determined by next-generation sequencing of the 16S rDNA. A preliminary principal component analysis (PCA) of four individuals demonstrated that two participants shared similar microbial profiles while the remaining two participants displayed independent clustering. To our knowledge, this is the first study analyzing daily temporal changes in the gut microbiome of children with ADHD and ASD and attempts to relate those changes to diet and behaviour of the child. As we continue to sequence samples and analyze our data, findings will contribute to our understanding of the gut-brain connection.

P1-A-20: Brain circuits establishment underlying social behavior during zebrafish development

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The mechanisms underlying the onset of social interactions and the establishment of the underlying neural circuits are poorly understood. Our goal is to study these circuits during the neurodevelopmental window of social behavior appearance. Zebrafish larva, expressing a genetically-encoded Ca2+ sensor (GCaMP6) in all neurons, represents a powerful model to combine behavioral studies with whole brain optical imaging in live animals. Considering its small and transparent brain, the larvae can be longitudinally imaged by two-photon microscopy over the period of initiation of social interactions (first few weeks of development). To identify more precisely the establishment of early signs of social

behavior, we are performing a series of behavioral assays on free-swimming larvae in custom-3D-printed arenas, over the first few weeks of life. Meanwhile, to detect changes in the functional activity of developing neural networks that correlate with early signs of sociability, we are optically measuring the activity of nearly all circuits using Ca2+ imaging. Using closed-loop projection of social stimulus in head-restrained larvae, we are simultaneously recording calcium oscillations with fast, 3D, two-photon microscopy. We next aim to characterize a socially-induced tail movement response in order to combine with optical imaging. Our preliminary tests indicate that we can monitor circuit activity at the cellular level in larval zebrafish throughout the critical neurodevelopmental window. Considering that several neurological conditions, such as autism, are characterized by early social deficits, the identification of the neuronal networks involved in the development of sociability may provide insights into the onset of these conditions.

P1-A-21: Aging reveals deleterious cardiorespiratory and metabolic consequences of neonatal stress in female rats.

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Introduction: At menopause, loss of ovarian hormones increases the risk of diseases, including hypertension, sleep apnea, and obesity. While only a subpopulation of women presents those disorders, the factors underlying these different aging trajectories remain unknown. Here, we tested the hypothesis that exposure to stress during early life contributes to the emergence of cardiorespiratory and metabolic issues in aging females. Methodology: Following birth, female rats were raised under standard conditions (CTRL) or subjected to neonatal maternal separation (NMS; 3h/day from postnatal days 3 to 12). At 60 weeks of age, we measured the animals' 1) mean arterial blood pressure (MAP; "tail-cuff" method), 2) apnea frequency (whole-body plethysmography), 3) body mass index (BMI), and 4) neuronal activity of the paraventricular nucleus of the hypothalamus (PVH), using FosB expression. PVH is a key structure in the regulation of stress response having a strong influence on blood pressure. Results: Compared to CTRL, NMS rats presented 1) 12% higher MAP with 9% lower heart rate 2) 30% greater apnea frequency 3) 15% higher BMI 4) 50% more FosB neurons in the PVH region containing vasopressin-producing neurons. Conclusion: The cardiorespiratory and "obese-like" profiles observed are similar to those reported in menopausal women, thus, we conclude that neonatal stress contributes to the emergence of those disorders later in life. Ongoing experiments are exploring how estrogens contribute to this stress-related disruption. Support: FRQ-S (268346), RSRQ (2021-22), and the CIHR (RK)

P1-A-22: An investigation of adult hippocampal neurogenesis in the human brain with spatial transcriptomics

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BACKGROUND AND AIM: The existence of neurogenesis in the adult human hippocampus has been the subject of intense debate in recent years, fuelled by the publication of several conflicting reports regarding the neurogenic potential of the adult human dentate gyrus (DG). Here, we aim to provide new insight on the extent of this phenomenon in the human hippocampus at the transcriptomic level using spatially-resolved transcriptomics. METHODS: We used the 10X Genomics Visium Spatial Gene Expression platform on frozen hippocampal sections (Douglas-Bell Canada Brain Bank) from young and middle-aged male adults (n=4) to assess the spatial expression of various neurogenic markers within the subgranular zone (SGZ) of the DG. We also looked at the simultaneous expression of markers specific to neural stem cells, proliferative cells and immature granule neurons with fluorescent in situ hybridization (RNAscope; Advanced Cell Diagnostics) on sections of DG from infant, adolescent and middle-aged adult males. RESULTS: We identified the expression of neurogenic markers in Visium capture spots located within and outside of the neurogenic niche in the adult DG. Using RNAscope, we visualized DCX expression in non-neurogenic cell types and brain regions, and an age-related increase of neurons expressing immature neuronal markers in adult subjects. CONCLUSION: Our findings reveal the presence of a pool of immature granule neurons in the adult human hippocampus, while suggesting that DCX expression in the human DG may not be specific to neurogenesis.

P1-A-23: Sex differentiation of the hypothalamic vasopressin system occurs during embryonic neurodevelopment

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Biological differences between men and women contribute to many sex-specific behaviors and disorders. Historically, such differences were largely, if not exclusively, thought to be due to hormone secretions arising from the gonads. Current dogma about the brain sex differences states that a surge in testosterone from the testis around birth masculinizes the male brain, with embryonic (E) neural development thought to occur in a sex-agnostic manner. However, we found that the hypothalamic vasopressin (AVP) system was sex dimorphic at the earliest stage of neurodevelopment, with males displaying more AVP+ neurons and protein from E13.5 and higher Avp transcripts from E12.5 in the hypothalamus, long prior to perinatal testosterone secretion. Furthermore, birthdating experiments showed higher numbers of AVP+ neurons born in males at peak neurogenesis (E11.5) compared to females. Mechanistically, we tested the functional requirements of Estrogen Receptors (ERs) in mediating embryonic sex differentiation. ER2 and GPER expression was higher in males than females by E11.5 in the hypothalamus and an ER2-selective inhibitor significantly reduced the number of primary neurospheres grown from isolated male 12.5 hypothalamic progenitors but not female. Combined, we propose that neural sex differentiation begins mid-gestation in the embryo in response to estrogen signaling. These findings also raise intriguing questions as to from where the masculinizing cue arises if the gonads have not yet differentiated to secrete sex hormones.

P1-A-24: The role of P2X7 in the development of the Fmr1-knockout mouse hippocampus

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Fragile-X Syndrome is the leading genetic cause of intellectual disability among children. Caused by the silencing of the Fmr1 gene on the X-chromosome, the subsequent reduction of FMR1 protein production leads to several neurodevelopmental problems. Mechanisms underlying these problems have been studied in the Fmr1-knockout mouse model, and much research has focused on the hippocampus. Hippocampal neurogenesis and synaptic plasticity have been found to be dysregulated in this model. The purinergic signalling pathway largely mediates the contribution of glial cells to these processes. Our lab has discovered that some receptors in the P2 receptor family are impacted in the Fmr1-knockout mouse cortex, altering astrocyte-mediated synaptogenesis. However, it is unknown if they are also affected in the hippocampus. My work has found that the expression levels of the P2X7 receptor are reduced in the Fmr1-knockout mouse hippocampus during synaptogenesis and synaptic plasticity periods. Specifically, this expression reduction occurs in newly formed neurons. Interestingly, the P2X7 receptor is known to halt neurite outgrowth and induce synaptic depression. Further work will examine the contribution of P2X7 to these aspects of Fmr1-knockout hippocampal neuron development, culminating in examining how P2X7 contributes to the overall development of the Fmr1-knockout hippocampal neural network.

P1-A-25: LRIG1 controls proliferation of adult neural stem cells

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In the adult mammalian brain, adult NSCs (aNSCs) are found in two specialized niches and exist in large part in a quiescent state. aNSCs in the ventricular-subventricular zone (V-SVZ) are activated from quiescence to produce olfactory bulb interneurons for brain maintenance and to repair the brain, in a limited manner, following injury. The mechanisms which control the activation of aNSCs from the quiescent state are not fully understood. Previous work from our lab has demonstrated that a protein called Leucine-rich repeats and immunoglobulin-like domains protein 1 (LRIG1) is important for limiting proliferation of radial precursor cells in the embryonic neocortex to enable a portion of these cells to become aNSC. The functional role, however, of LRIG1 in the control of proliferation/quiescence of aNSCs remains poorly understood. Using LRIG1 knockout mice and immunohistochemistry (IHC) we show that NSC proliferation is increased when LRIG1 is lost, without impacting neuronal progeny. Mechanistically, in the embryo, LRIG1 functions by modulating the epidermal growth factor receptor (EGFR), however we demonstrate that LRIG1 does not modulate this pathway in adult NSCs. Making use of RNA-sequencing, IHC and culture studies we show that LRIG1 likely controls aNSC proliferation through the TGFβ superfamily. Understanding how LRIG1 controls the activation of aNSC through this pathway, could enable more robust brain repair.

P1-A-26: Cadherin 13 expression in somatostatin-positive interneurons regulate auditory sensory processing

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Cadherin-13 (CDH13), a unique glycosylphosphatidylinositol-anchored member of the cadherin family, has been identified as a risk gene for psychiatric conditions, such as attention-deficit/hyperactivity and autism spectrum disorders. In the hippocampus, CDH13 expression is restricted to GABAergic interneurons (INs) and its global deletion affects basal inhibitory transmission. However, whether CDH13 expression specifically in GABAergic cells affects cortical network function and cognition is unknown. By using single cell transcriptomics, we found that CDH13 mRNA is highly enriched in cortical somatostatin-expressing (SST+) GABAergic INs in juvenile mice. We then analysed the expression pattern of CDH13 in cortical parvalbumin-expressing (PV+) and SST+ INs, by using RNAscope. To test whether CDH13 expression in different INs contributes to specific cognitive impairments, we generated conditional knockout mice where CDH13 was selectively deleted in SST+ (SST-Cre; Cdh13LoxP/LoxP; SSTcKO mice) or in PV+ GABAergic INs (PV-Cre;Cdh13LoxP/LoxP ;PVcKO mice). By performing in vivo intracortical recording from awake mice, we identified specific and significant alterations in multiple aspects of auditory processing, including reduced habituation to repetitive auditory stimuli, faster dynamics of mismatch negativity and increased P300 component, which is thought to be associated with attentional processing, in SSTcKO mice. Conversely, we found no alteration in auditory processing in PVcKO mice. Taken together, our results indicate that SST+ INs specific CDH13 expression regulates auditory processing. Understanding cell-specific alterations caused by CDH13 deficiency in mouse models may ultimately shed light on the pathophysiology underlying specific psychiatric symptoms.

P1-B-27: In vivo Ca2+ imaging of astrocytes and oxytocin neurons in the hypothalamic paraventricular nucleus

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In the hypothalamic paraventricular nucleus (PVN), neurons and astrocytes exist in a structurally compact microenvironment where bidirectional communication between the two cell types influences the physiological and behavioural output. Oxytocin (OT) neurons in the PVN are known to be strongly activated by social stimuli. Furthermore, stress stimuli increase circulating OT levels, suggesting that OT neurons are also activated by stress. Astrocytes are ubiquitous glial cells that respond to/regulate neuronal activity. Little is known about how social or stress stimuli individually influence PVN astrocyte and OT neuron activity and potentially modulate their interactions. To begin to examine this, we expressed genetically encoded calcium (Ca) reporters in PVN astrocytes and OT neurons (GCaMP6f and RCaMP2, respectively) and performed dual-channel fiber photometry to record in vivo population activity in freely behaving mice (n=10). Social sniffing of conspecific stimulus mice induced a large Ca transient in OT neurons, beginning ~2s before sniffing initiation and peaked between 1-2s after. The observed Ca signal increase in OT neurons was of a larger magnitude and more sustained while sniffing a

familiar mouse vs. an unfamiliar mouse. In astrocytes, both sniffing of familiar and unfamiliar mice induced small increases in Ca transients. Stress stimuli presented as looming shadows robustly increased astrocyte Ca signal, beginning during initial shadow appearance (first 3s) and peaking during the looming phase (last 3s). A smaller and more sustained Ca increase was observed in OT neurons in response to the stimulus. Our results suggest that, while both cell types are responsive to both stimuli types, the magnitude of evoked Ca signal varies in a stimulus-dependent manner.

P1-B-29: Autolysosomal exocytosis of lipids protect neurons from ferroptosis

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During oxidative stress neurons release lipids that are internalized by glia and stored in lipid droplets. This process is essential to maintain the health and function of the nervous system. Defects in this coordinated process play an important role in several neurodegenerative diseases. Yet, the mechanisms of lipid release and its consequences on neuronal health are unclear. Here, we demonstrate that lipid-protein particle release by autolysosome exocytosis protects neurons from ferroptosis, a biochemically distinct form of cell death driven by lipid peroxidation. During oxidative stress in primary cell culture or fly retina, neuronal lipid release depends on the exocytic machinery; VAMP7 and syntaxin 4. We show that these lipids are released through exocytosis of autolysosomes. We observe membrane-bound lipid-protein particles by transmission electron microscopy and demonstrate these particles are released from neurons using cryo-electron microscopy. Failure to release these lipid-protein particles causes lipid hydroperoxide accumulation and cell death by ferroptosis. Our results reveal how neurons use autolysosomal exocytosis to rid themselves of peroxidated lipids generated during oxidative stress. Given the number of brain pathologies that involve ferroptosis, defects in this pathway likely play a key role in the pathophysiology of neurodegenerative disease.

P1-B-30: Molecular determinants of dorsal horn excitability and pain processing in male and female rats and humans

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Chronic pain represents a debilitating healthcare challenge. While females report more incidences of pain, most pain research has not been sex inclusive. Thus sex-specific therapeutics remain unexplored. To address this, we characterized the expression of molecular determinants of a canonical dorsal horn hyperexcitability pathway across sex. Brain derived neurotrophic factor-tyrosine kinase B (BDNF-TrkB) signalling drives disinhibition, coupling to increased excitatory N-methyl-D-aspartate receptor (NMDAR) activity only at male dorsal horn synapses. We explored whether differences in baseline expression of

key players (such as the BDNF receptor,TrkB; potassium-chloride cotransporter 2, KCC2; and FYN kinase) in this pathway account for sexually dimorphic pain processing across species. We employed RT-qPCR and western blot approaches on micro-dissected regions of spinal cord to quantify expression profiles in the superficial dorsal horn (pain-processing;SDH) versus deep dorsal horn (other somatosensory modalities; DDH). Viable cord tissue was collected from adult (3-4 months) male and female Sprague Dawley rats (n=8/sex) and adult (20-70 years) human donors. Our findings suggest that distinct determinants of dorsal horn excitability, such as TrkB and KCC2, have differential relative expression in the SDH and DDH, both by target and region. Preliminary analysis suggests potential sex differences in the SDH/DDH expression ratio for select players. Differential expression predisposes the SDH to hyperexcitability; understanding these spinal mechanisms may help identify future pain therapeutic targets that are effective across sex and species.

P1-B-31: Alterations in erythrocyte membrane fatty acids in bipolar disorder

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Cell membrane abnormalities have been implicated in the pathophysiology of bipolar disorder (BD), with membrane lipid defects reported in the brain and peripheral tissues in BD. Red blood cell (RBC) membrane fatty acid composition parallels that of neural membranes; as such RBCs may provide a valid model for investigating brain membrane abnormalities in BD. The current study investigated RBC fatty acid composition in BD compared to community controls. In the same sample, we have previously studied brain microstructure using diffusion MRI, showing lower mean kurtosis (MK) in several brain regions in the BD group. Here, we examined correlations between RBC fatty acids and MK to determine if RBC fatty acid composition might be associated with white matter microstructure in BD. The fatty acid composition of RBC membranes in BD (n = 28) and control (n = 27) was determined by gas liquid chromatography. The average MK values of the whole brain white matter were determined for each subject, then a general linear model-based analysis using in-house MATLAB scripts was used to examine the relationship between RBC fatty acids and MK. BD was associated with higher RBC monounsaturated fatty acid (oleic acid + nervonic acid) and lower RBC plasmalogen (C16DMA + C18DMA) levels. Positive correlations were found between RBC nervonic acid, plasmalogen, eicosapentaenoic acid, lignoceric acid, and MK in the BD, but not the control group. Our results indicate the presence of RBC membrane abnormalities in BD, which may be associated with white matter microstructure in BD.

P1-B-32: Inflammation-induced LTP impairments are rescued by L-type calcium channel antagonism

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Multiple sclerosis (MS) is the most prominent debilitating neuroinflammatory disorder affecting young people in North America, and many patients suffer from cognitive impairment. The hippocampus is critically involved in synaptic plasticity, such as long-term potentiation (LTP), a calcium (Ca2+)-dependent process that is widely considered as a molecular substrate underlying learning and memory. In MS, the

hippocampus is demyelinated, inflamed, and atrophied with structural and functional pathology visible in early stages. Ca2+ enters cells through several channels, including L-type Ca2+ channels (LTCCs) that are expressed on both neurons and glial cells. Importantly, LTCC expression increases in response to inflammation in both neural and astrocytic cultures. Although FDA-approved LTCC antagonists are commonly used to treat hypertension and stroke, they have not been tested in MS patients. Herein we induced an inflammatory response in acute hippocampal slices using either lipopolysaccharide (LPS) or a cocktail of MS-relevant pro-inflammatory cytokines (IL-1β, TNF, IFNγ, CXCL10) and measured LTP via extracellular recordings in the Schaffer collateral pathway. A 2hr exposure to LPS or 90min exposure to cytokine cocktail resulted in reduced LTP. In both inflammatory conditions, 20μM of the LTCC antagonist nifedipine normalized LTP to control levels. These results suggest that antagonism of LTCCs may offer a novel therapeutic avenue for dual treatment of both inflammation and cognitive impairment in MS.

P1-B-33: Generation of microglia using direct reprogramming to study microglial aging

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Microglia are the resident immune cells of the central nervous system (CNS), and they are essential for proper brain functioning and homeostasis. With age, they adopt a dystrophic morphology which is accompanied by a disruption in their homeostatic functions. Microglial dysfunction associated with aging is believed to contribute to the progression of neurodegenerative disorders such as Parkinson's disease. However, how aging confers to microglia these phenotypical changes is still unknown, especially in humans given the lack accessibility of live CNS cells for molecular work. As such, we aim to develop a system in which the effect of aging on microglial function can be studied in human microglia. To do so, we used two different approaches: the chemical induction of senescence and the overexpression of progerin, a truncated form of lamin A associated with premature aging in an immortalized cell line of human microglial-like cells as well as in microglia derived from human induced pluripotent stem cells (iPSCs). The results obtained with the immortalized microglia-like cell line show that the combined exposure to the "senescence cocktail" induces age-related features characterized by the increase in double-stranded DNA breaks, increased DNA damage related to oxidative stress, elevated level of senescence associated-b -Galactosidase, enlarged nucleus as well as lower cell proliferation. On the other hand, the overexpression of progerin only induced the formation of double stranded DNA-breaks in these cells. Our results suggest that cellular aging can be chemically induce in microglia-like cells, providing a new model to study the impact of aging on microglial functions.

P1-B-34: NaV1.1 Selective Potentiators Increase PV+ Fast-Spiking Interneuron Excitability, Normalize Inhibition/Excitation Imbalance and Restore Motor Performance in a Mouse Model of Dravet Syndrome.

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Loss-of-function variants of SCN1A cause Dravet Syndrome and generalized epilepsy with febrile seizures plus (GEFS+), by decreasing Nav1.1 expression and function of inhibitory interneurons. The resulting hypo-excitability of interneurons reduces inhibitory input onto excitatory neurons, leading to epilepsy and other co-morbidities. To date, there are no subtype selective potentiators of Nav1.1 channels clinically available that directly address the underlying mechanisms of the disease. We have identified potent, isoform-selective, brain penetrant small molecule potentiators of NaV1.1 channels with good drug-like properties that increase Nav1.1 current and restore the firing activity of parvalbumin-expressing, fast-spiking GABAergic interneurons in Dravet Syndrome mice (Scn1a+/-). The firing properties of excitatory neurons were not affected by the compounds. Wild-type interneurons were similarly not affected by the compound. Furthermore, we also show that the compounds normalize the imbalance in spontaneous excitatory and inhibitory synaptic input to pyramidal neurons in Scn1a+/- mice. When tested in vivo, these compounds suppress seizures in an Scn1a+/- mouse 6 Hz seizure model and improve motor dysfunction in the rotarod assay. In conclusion, our precision medicine approach, that specifically targets the pathophysiological deficit in Dravet Syndrome, may provide a novel approach to control seizures and to ameliorate other co-morbidities.

P1-B-35: Impaired synaptic plasticity in juvenile conditional STAT3 knockout mice

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Synaptic plasticity is regarded as the underlying cellular mechanism of learning and memory. Activity-dependent changes that lead to increases or decreases in the strength of synaptic connections are called long-term potentiation (LTP) and long-term depression (LTD), respectively. Our lab previously demonstrated that Signal Transducer and Activator of Transcription 3 (STAT3) is necessary for LTD in the rat hippocampus by using pharmacological and knockdown approaches. The current work aims to further understand the role of STAT3 in synaptic plasticity through genetic, cell-selective deletion. STAT3 conditional knockout (cKO) mice were generated through floxed Stat3 mice carrying Emx1-IRES-cre to drive excision beginning in embryonic development. CA3-CA1 field excitatory postsynaptic potentials were recorded from the stratum radiatum in hippocampal slices from 2-3-week-old mice. LTD induced by either low frequency stimulation or 3 minutes of 20µM NMDA was unaffected in the cKO. Lastly, LTP was measured using two induction protocols: compressed and spaced theta burst stimulation, cTBS and sTBS, respectively. Each consisted of 25 pulses, repeated 3 times, but differ in their inter-burst intervals (10 s versus 10 min) and are thought to engage distinct LTP expression mechanisms. LTP induced by sTBS was unaffected in the cKOs, whereas LTP following cTBS was significantly lower in cKO slices compared to controls. Together, these results suggest a differential role of STAT3 in LTD versus LTP in juvenile mice and highlight the complexity of synaptic plasticity mechanisms.

P1-B-36: The molecular mechanisms of glycolytic enzyme palmitoylation in neurons

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Neuronal axons can reach staggering lengths of over a meter, making the efficient transport of essential proteins, organelles, and vesicles a daunting challenge. But, as it turns out, this process is crucial in preventing neurodegenerative and neurodevelopmental disorders. Recent research has uncovered a key player in this transport system: glycolytic enzymes. These enzymes, which provide the energy needed for transport in the form of ATP, are attached to fast transport vesicles that are propelled by motor proteins dynein and kinesin. But, the question remains, how do these soluble, cytosolic enzymes attach to fast moving vesicles? I discovered that a post-translational modification called palmitoylation may hold the answer. I found that seven out of the ten glycolytic enzymes are palmitoylated in vivo, with six predominantly palmitoylated in the nervous system. I hypothesize that palmitoylation acts as a tether, attaching the enzymes to transport vesicles where they provide the necessary "on-board" energy for transport. To test my hypothesis, I will knockdown specific glycolytic enzymes and replace them with palmitoylation-resistant variants in neurons, and then use fluorescent labeling to track their attachment to vesicles and movement. Unlocking the mechanisms behind this process not only improves our understanding of neurodevelopment and physiological neuron function, but also has the potential to shed light on complex behaviors like learning and memory.

P1-B-37: Conserved features of electrical and calcium signaling in single cell eukaryote and choanoflagellate, Salpingoeca rosetta

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Single cell choanoflagellate, Salpingoeca rosetta, of 5 microns in length, contain gene homologs for ion channels, transporters, transcription factors, and scaffolding proteins. associated with electrical and calcium signalling. In the presence of Algoriphagus bacteria, S. rosetta undergoes developmentally programmed cell divisions to form a multicellular "rosette" cluster. 10 microVolt, electrical potentials of spike width of average 7 ms with a variable "calcium plateau" appear on a Med64 microelectrode array, upon induction of multicellularity. Contributors to the spontaneous electrical potentials include gene homologs: SroNaV2, SroCaV1, SroCav3, SroKV and SroHCN, representing 67 human ion channel genes. Expressed in human cell lines, SroNaV2 exhibits a lidocaine-sensitive, voltage-dependent, and non-selective currents, with slow kinetics. SroCaV1 exhibits a nifedipine-sensitive, high voltage-activated, calcium-selective current, like Cav1.2. A modified patch clamp reveal isolated ion currents in "primed" S. rosetta, that are consistent with in vitro expressed ion channels. Our laboratory has created an inventory of 38 peptide polyclonal antibodies which reveal a highly dynamic and changeable expression of ion channels and other proteins in different life stages including immobile thecate, slow and fast swimmers, asexually dividing "chains" and multicellular "rosettes". S. rosetta at different life stages forms a calcium channel and RIM-BP complex like presynaptic nerve terminals, a CRAC channel complex between STIM and Orai, muscle-like co-clustering of the calcium channel complex with the ryanodine receptor, and a colocalization with transcription factor, CREB1 in the nucleus associated with synaptic plasticity and long-term potentiation.

P1-B-38: The cell-type-specific organization of the anterior thalamic nuclei of the mouse brain

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Understanding the heterogeneity of neural cell types is crucial to unravelling the intricacies of the cellular mechanisms of learning and memory. Recently, we have uncovered atypical and slow memory-like activity in a specific population of mouse subiculum neurons that connect to the anterior thalamic nuclei (ATN). From this finding, we were motivated to understand whether the ATN may have a similarly specific population of neurons that receives subiculum input and participates in memory. To pursue this goal, we first used single-cell RNA sequencing (scRNA-seq) and Visium spatial transcriptomics to establish ATN subregions with unique transcriptional profiles. We found that all ATN neurons were excitatory, and formed 3 spatially and transcriptomically distinct clusters. We then employed multiplexed fluorescent in situ hybridization (mFISH) targeting 8 marker genes to map out the molecular-cellular landscape of the ATN at a single-molecule and single-cell resolution. Using dimensionality reduction and hierarchical clustering, we discovered transcriptomically distinguished clusters in and around the ATN, corresponding to the anterodorsal (AD), anteroventral (AV) and anteromedial (AM) nuclei and the surrounding excitatory neurons. Across the anterior-posterior axis, the marker genes for each subtype were selectively expressive in their corresponding ATN subregion. Furthermore, our data revealed 2 distinct subpopulations of excitatory neurons in the AV, which parcellated into 2 regions along the mediolateral axis. The spatial heterogeneity within the ATN can be used in the future to examine unresolved memory circuits within the brain.

P1-B-39: TRIM32-mediated type I interferon signaling causes tactile hypersensitivity in mice lacking translational repressor 4E-BP1 in Nav1.8-positive sensory neurons

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mTOR is a highly evolutionarily conserved serine/threonine kinase that regulates cell homeostasis through key cellular processes, including cell growth and proliferation, mRNA translation, autophagy, and cytoskeleton organization. mTOR is present in two structurally and functionally distinct multiprotein complexes: mTORC1 (mTOR Complex 1) and mTORC2. The activity of mTORC1 was shown to promote pain hypersensitivity, but the specific mechanism remains unknown. mTORC1 regulates the rate of eIF4E-dependent mRNA translation via inhibition of translational repressor 4E-BP1. To understand the underlying mechanism, we selectively ablated 4E-BP1 in Nav1.8-positive neurons (4E-BP1 cKO). We then assessed behavioral phenotypes and DRG neuron excitability, as well as performed translating ribosome affinity purification (TRAP) to study differentially expressed genes (DEGs) in sensory neurons. Our behavioral experiments demonstrated that 4E-BP1 cKO mice exhibit basal tactile hypersensitivity but no

thermal phenotypes. Profiling gene expression in sensory neurons lacking 4E-BP1 (using TRAP approach) revealed changes in pathways involved in antiviral responses. Follow up experiments showed TRIM32-mediated increase in type I interferon signaling. Blocking interferon receptors reversed the tactile hypersensitivity and neuronal excitability in 4E-BP1 cKO mice. Our study demonstrates the central role of eIF4E-dependent translational control in Nav1.8-positive sensory neurons in regulating mechanical sensitivity. Moreover, our results indicate that ablation of 4E-BP1 in these neurons increases the translation of TRIM32 which promotes interferon-mediated tactile allodynia.

P1-B-40: Immune-related transcriptomic and epigenetic reconfiguration in microglia after LPS exposure: an omics integrative study.

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Molecular alterations affecting microglia activity have been consistently associated with the inflammatory response. These cells can have pro or anti-inflammatory activity, phenotypes partly induced by epigenetic mechanisms. Here, we explored the epigenetic landscape of BV2 cells, its modifications during inflammation and its relationship with the inflammatory transcriptomic profile. Through CUT&RUN, we profiled four genome-wide histone marks (HM) (H3K4me1, H3K4me3, H3K27ac and H3K27me3) in lipopolysaccharide exposed-cells and compared their distributions to control cells. Transcriptomic profiles were determined through RNA-seq and differentially expressed genes were identified and contrasted with the epigenetic landscapes. Other downstream analyses were also included in this study. We observed that the combination of H3K4me1, H3K27Ac and H3K4me3 was the most common state across the genome, whereas only the two latter marks constitute the state most frequently seen in promoters. We also found that the differentially bound "active" regions were strongly described by immunological-related terms ("defense to", "response to"). Additionally, the association between differentially expressed genes involved and HM patterns was assessed. Strong correlation between H3K27me3 and lower gene expression was observed, and active marks were related to a higher expression. This study exhibits a likely epigenetic-dependant reconfiguration of BV2-cells that leads to the inflammatory response.

P1-B-41: Glutamatergic neuronal activity stimulates astrocytic fatty acid catabolism

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Lipid droplets are organelles that store fatty acids as neutral lipids. Fatty acids are released from lipid droplets to address the metabolic needs of cells. This includes providing fatty acids to be oxidized in the mitochondria for energy production. We previously discovered that astrocytes respond to the excitatory neurotransmitter glutamate by decreasing the number of lipid droplets and transporting fatty acids to the mitochondria. But how glutamate signals to regulate fatty acid metabolism in astrocytes and whether the net result is increased ATP production is unknown. Here, we show that glutamate stimulates phosphorylation of AMP-activated protein kinase and acetyl-coA carboxylase, two signaling proteins

associated with mitochondrial fatty acid oxidation. Consistently, using metabolic flux assays, we found that glutamate increased mitochondrial respiration rates, mitochondrial ATP, and total ATP production. Our work indicates that glutamatergic neuronal activity stimulates fatty acid oxidation in neighbouring astrocytes and provides a better understanding of how lipid homeostasis is coupled between the two cell types.

P1-B-42: Regulation of subfornical organ neurons by the cytokine interleukin-6

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The subfornical organ (SFO) is a sensory circumventricular organ that contributes to autonomic and cardiovascular regulation by detecting circulating signaling molecules, hormones and cytokines, and communicating this information to hypothalamic centres. Previous studies indicate that SFO neurons respond to interleukin-6 (IL-6), a pleiotropic cytokine, however the electrophysiological mechanisms have not been investigated. Whole-cell patch clamp recordings were performed on coronal brain slices containing SFO neurons from male SD rats. Application of 100 ng/mL IL-6 caused depolarization in 39.4% (n=13;8.8 ± 2.7 mV) and hyperpolarization in 24.2% of neurons (n=8;-7.4 ± 1.4 mV). IL-6 caused a concomitant increase or decrease in action potential frequency. Non-responder cells tended towards no change in input resistance. However, in responder cells the change was not correlated with hyperpolarization or depolarization, suggesting modulation of multiple pathways. Our results are consistent with previous literature that showed intravenous injection of IL-6 caused activation of SFO neurons, but our data also suggests that IL-6 hyperpolarizes the membrane potential of an additional subset of SFO neurons. Our results indicate that IL-6 modulates electrical properties of SFO neurons, however, the mechanisms that underly the hyperpolarization and depolarization need further characterization. We show that the SFO has a key function in detecting circulating IL-6, and is an area of importance when aiming to understand inflammation caused by IL-6 release during homeostatic challenges.

P1-B-43: Unique intrinsic properties shaping the cellular computations of a novel excitatory cell type in the subiculum

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Understanding the extent to which cellular computations vary in a cell-type-specific manner is critical for interpreting information processing in the brain. A novel excitatory cell type in the deepest layer of the subiculum - non-pyramidal "deep" cells - exhibit a striking a lack of radial oblique dendrites, higher input resistance, and sustained spiking activity. This suggests that deep cells are able to perform unique cellular computations relative to classical pyramidal subiculum cells. Here, we built computational models from morphologically reconstructed pyramidal cells and deep cells to investigate the differences in intrinsic properties between these cell types, and how this shapes their computations. Morphological

analyses of tuft and basal dendrites revealed that deep cells have markedly different dendritic complexity, branch numbers, and branch lengths relative to pyramidal cells. We also found that deep cells exhibited more spiking and a lower threshold for spiking in response to tuft and basal synaptic inputs. Further, pyramidal cells that lacked radial oblique dendrites exhibited input resistances and synaptic responses biased towards those of deep cells. Lastly, we investigated interactions of concurrent basal and tuft synaptic inputs, and identified that these two types of input drive supralinear summation in deep cells. Together, our research reveals specialized computational and intrinsic properties of deep cells that support cell-type-specific information processing in the subiculum.

P1-B-44: Pannexin-1 opening in cytotoxic edema triggers neuronal death but also provides secondary protection via microglia recruitment

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Neuronal swelling during cytotoxic edema is triggered by Na+ and Cl- entry and is Ca2+-independent. However, the causes of subsequent neuronal death after swelling are a longstanding puzzle. We tested if the large-conductance Pannexin-1 (Panx1) channel contributes to cytotoxic death and whether ATP release through Panx1 mobilizes microglia towards swelling neurons. Panx1 channel inhibitors reduced and delayed neuronal death when swelling was triggered by intense voltage-gated Na+ entry and subsequent Cl- entry. We show that oxidative stress from reactive oxygen species (ROS) occurred in neurons during swelling and that increased ROS caused cytotoxic Panx1 opening. ROS activated Panx1 currents in whole-cell recordings and ROS scavengers inhibited Panx1 currents and were neuroprotective in swelling assays. Panx1 opening and subsequent ATP release recruited microglial processes to contact swelling neurons. Depleting microglia using the CSF1 receptor antagonist PLX3397 or blocking P2Y12 receptors exacerbated cytotoxic death of neurons suggesting that the Panx1- and ATP-dependent enhancement of surveillance by microglia is neuroprotective. We conclude that cytotoxic edema triggers oxidative stress in neurons that in turn opens Panx1 to trigger neuronal death, but also initiates neuroprotective feedback mediated by microglia contacts.

P1-B-45: Effects of ketamine enantiomers and their HNK metabolites on hippocampal synaptic transmission and plasticity

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Ketamine, an anesthetic and recreational psychedelic, at lower doses acts as a rapid and persistent antidepressant after a single dose in patients with treatment-resistant major depressive disorder. While several hypotheses have been proposed to explain its acute action, the mechanism underlying its persistent effect is unknown and there is controversy about whether ketamine acts directly or via its metabolism to (2R,6R)-hydroxynorketamine (HNK). Extending our previous work (Kang et al., 2020; PMID: 33088919), we explored whether ketamine itself, as an NMDA receptor (NMDAR) antagonist, has synaptic effects that could explain its long-lasting antidepressant action independent of (2R,6R)-HNK.

Using CA3-CA1 field potential recordings in stratum radiatum of mouse hippocampal slices, we show that (S)- and (R)-ketamine substantially inhibited synaptic NMDAR-mediated responses and LTP, without affecting basal AMPA receptor (AMPAR)-mediated transmission. Surprisingly, we found that a short (20 min) application of (S)-ketamine leads to a sustained depression of NMDAR-mediated transmission that persists after drug washout. Conversely, the ketamine metabolites (2S,6S)- and (2R,6R)-HNK had only minor effects on NMDAR transmission and plasticity and, in contrast to previous reports, did not modulate basal AMPAR transmission or paired-pulse facilitation. Together, our findings suggest that a long-lasting modulation of synaptic NMDAR function may contribute to ketamine's sustained actions, independently of its metabolism to HNK.

P1-B-46: Brain State Dependent Organization of Claustrum Neurons Innervating the Retrosplenial Cortex

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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 hindered 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 across sleep and locomotion. With this methodology, we present a characterization of cell specific retrosplenial-cortex-projecting claustrum neuron activity through the sleep-wake cycle coupled with local field potential and pupil recordings. Preliminary data suggests the CLA-RSP pathway is most active during slow wave sleep and quiet awake states. A subset of axons exhibit activity correlated with periods of low slow wave power during microarousals, however most claustrum activity is correlated with high slow wave power and low arousal. Collectively, our data indicates that claustro-retrosplenial cells exhibit brain-state specific activity patterns and are preferentially active during synchronized or low arousal states. In addition, heterogenous responses to brain state suggest that different subpopulations of claustrum neurons may have different roles in shaping downstream cortical activity.

P1-B-47: Elucidating the mechanism underlying mGluR-LTD deficit in synaptopodin-deficient mice

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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. Recently, we have shown that SP is critically involved in

the regulation of structural plasticity during mGluR-LTD. It is very important to also assess the effect of SP on the functional aspect of mGluR-LTD. Here, by using field recording, we show that hippocampal mGluR-LTD is impaired in SPKO. To further elucidate the mechanisms underlying mGluR-LTD deficit in the absence of SP, we looked at mGluR1/5 activity and their localization through electrophysiology and imaging techniques. We found that mGluR-LTD in SPKO has reduced mGluR5 activity, which is not due to decreased level or mislocalization of mGluR5. Interestingly, we found that the mGluR1/5 scaffolding protein SHANK3 level and spine localization are reduced in SPKO, suggesting that impaired membrane insertion of mGluR1/5 could attribute to mGluR-LTD deficit in SPKO. Furthermore, we found that mGluR-LTD becomes protein synthesis-independent in SPKO and that the remaining mGluR-LTD in SPKO is mediated through presynaptic mechanisms. From this work, we show that the lack of SP switched mGluR-LTD from a postsynaptically driven event to a presynaptically driven event.

P1-B-48: A stereological assessment of cerebellar astrocytes in mice, macaques, and humans

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Objective: Cortical astrocytes are a heterogenous glial cell population; however, less is known about hindbrain regions. Using a stereological approach, we quantified astrocytes and Purkinje cells (PCs) in functionally distinct cerebellar regions. Methods: Lobule III (motor), Crus I (cognitive), and vermis VIIA folium (emotion) regions of the cerebellum were sampled in transgenic mice (ALDH1L1-Cre/ERT2; Rosa26-TdTomato), cyno macaques, and healthy humans (Douglas-Bell Canada Brain Bank). Sagittal sections were labelled for canonical astrocyte markers glial fibrillary acidic protein (GFAP) and aldehyde Dehydrogenase-1 Family member L1 (ALDH1L1). GFAP immunoreactive (-IR) and ALDH1L1-IR astrocytes were counted using stereology in the Purkinje cell layer (PCL), granule cell layer (GCL), and white matter (wm). PCs were also quantified. Cavalieri Method was used to measure volumes. Results: In humans, lower astrocyte and PC densities were observed in the vermis compared to lobule III and Crus I. Crus I had the highest Bergmann glia (BG): PC ratio. Compared to macaques and mice, humans displayed increased astrocyte densities in the PCL and GCL. We observed an opposing trend for ALDH1L1-IR and GFAP-IR astrocytes whereby ALDH1L1-IR astrocyte densities increased with species evolution while GFAP-IR astrocyte densities decreased. Conclusions: These results suggest that in humans, astrocyte densities are heterogeneous across functionally distinct cerebellar regions, possibly indicative of a role for these cells in higher level cognitive and emotional cerebellar processing.

P1-B-50: Neuronally secreted chemokine fractalkine enhances oligodendrogenesis and remyelination from CNS precursor cells

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Multiple Sclerosis (MS) is an autoimmune and neurodegenerative disorder that leads to the damage or loss of myelin, an insulating layer that coats and protects nerve axons, and myelin-producing cells, oligodendrocytes. Current disease-modifying therapies are ineffective for progressive MS, which is characterized by worsening of the disease with no improvement. Treatments for progressive MS could be achieved by stimulating the production of new oligodendrocytes from resident oligodendrocyte precursor cells (OPCs) scattered throughout adult brain tissue. These newly formed oligodendrocytes would in turn remyelinate the brain. Our lab has shown that chemokine fractalkine (FKN) stimulates oligodendrogenesis in the normal adult brain from neural stem cells (Watson et al. 2021 Stem Cell Rep). Here, we asked whether fractalkine enhances oligodendrogenesis and remyelination from parenchymal OPCs after a demyelinating injury. Using cuprizone mouse model of demyelination, we show that infusion of fractalkine (CX3CL1) into the brain after demyelinating injury increases de novo oligodendrocyte formation and enhances remyelination in the corpus callosum (white matter tracts) and cortical grey matter (de Almeida and Watson et al. 2023 Stem Cell Rep). We further show this is achieved by increased OPC proliferation in the cortical grey matter and by attenuation of microglia/macrophage activation both in corpus callosum and cortical grey matter. Finally, we show activated OPCs and microglia/macrophages express fractalkine receptor CX3CR1 in vivo, and that in OPC-microglia co-cultures fractalkine increases in vitro oligodendrocyte differentiation by modulating both OPC and microglia biology. Thus, our results demonstrate a novel, pro-regenerative role of fractalkine after demyelination

P1-B-51: Effects of 17β-estradiol, progesterone, and allopregnanolone on evoked field excitatory postsynaptic potentials in layers II/III of the rat infralimbic cortex in vitro.

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Reproductive hormones can have effects on neuronal excitability and synaptic function in multiple brain areas, and application of estrogen in the prefrontal cortex can rapidly alter navigational strategy in female rats. The present study investigated the effects of 17ß-estradiol (E2), progesterone, and allopregnanolone on the infralimbic region of the prefrontal cortex. Brain slices were obtained from male and female Long-Evans rats (7 to 10 weeks old) for extracellular recordings. First, field excitatory postsynaptic potentials (fEPSPs) evoked by stimulation of layer I were recorded at multiple depths between the cortical surface and the corpus callosum at intervals of ~100 µm. A fast surface-negative fEPSP, attributable to rapid excitatory synaptic activation, was observed in layers II/III. A negative-going field component was also observed in layers V/VI at longer latencies, and likely reflects polysynaptic activation of deep layer neurons. Drug-effects on synaptic responses recorded in Layers II/III were assessed by recording fEPSPs during a 20 min baseline period, and during application of E2 (10 nM), progesterone (100 nM), or allopregnanolone (1 µM) for a 20 min period. Preliminary data show no significant effect of E2 or allopregnanolone on the amplitudes of fEPSPs, but do show that fEPSP amplitude increased during application of progesterone, and remained elevated during the 20-min washout period. These data point to a potential mechanism through which progesterone may modulate cognitive function within the prefrontal cortex.

P1-B-52: Comparison of N-methyl-D-aspartate Receptor Subunit Expression and Distribution in Dorsal Horn Pain Processing Circuits across Species and Sex

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Chronic pain is a debilitating disease that is poorly managed and more prevalent in women than men. More studies translating rodent pain mechanisms to humans are needed to develop effective pain therapies. N-methyl-D-aspartate Receptors (NMDARs) are key regulators of the hyperexcitability and central sensitization of nociceptive circuits in laminae I-II of the spinal cord superficial dorsal horn (SDH). Neuronal subpopulations within these laminae may express distinct subtypes of NMDAR subunits (GluN1/GRIN1, GluN2A-D/GRIN2A-D, GluN3A-B/GRIN3A-B), which confer different functional NMDAR properties and different mechanistic roles in shaping plasticity. To investigate GRIN gene expression across species, laminae and neuronal subtypes, we used two studies: a meta-analysis of 6 mouse spinal cord single cell RNA sequencing (sc-RNAseq) data (Russ et al, 2021, Nat Commun), and a study that performed sc-RNAseq on highly viable spinal cord tissue from 7 organ donors. We also performed RT-qPCR and immunohistochemistry on adult male and female rat spinal cord tissue to compare GRIN gene and GluN2 protein expression across species, sex and laminar location. Our results indicate that GRIN gene and GluN2 protein expression is relatively well conserved across species and sex, with prominent expression of GluN1, GluN2A, GluN2B, and GluN2D subunits. GluN2 subunits are localized to the SDH in rats and humans but enriched in the lateral SDH in rats only. GRIN3A, an understudied NMDAR subunit, is also highly expressed in SDH circuits of mice and humans. These findings may uncover new mechanisms for synaptic plasticity in dorsal horn nociceptive circuits.

1-B-53: A lipid-gated non-selective cation current in Aplysia bag cell neurons is inhibited by Ca2+ and a precursor lipid

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Neuronal activity is influenced by non-selective cation currents, which in turn are regulated by lipid metabolites and Ca2+. The sea snail, Aplysia californica, lays eggs following an afterdischarge in the neuroendocrine bag cell neurons, which is driven in part by a diacylglycerol (DAG)-gated cation current. To understand how this current is controlled, cultured bag cell neurons were whole-cell voltage clamped and exposed to m-3M3FBS, which stimulates phospholipase C to hydrolyse phosphatidylinositol 4,5-bisphosphate (PIP2) into DAG. In accordance with cation channel opening, conductance was significantly higher at peak current, and a reversal potential of -25.1 mV was found by delivering a ramp voltage protocol. Low extracellular Ca2+, or replacing Ca2+ with Ba2+, potentiated the m-3M3FBS current. Depletion of PIP2 with wortmannin, an inhibitor of PIP2 synthesis, potentiated current stimulated by a soluble analog of DAG. We suspect that the DAG-stimulated current is carried by an Aplysia TRPC5. Real-

time quantitative polymerase chain reactions showed the relative expression of Aplysia TRPC5 appeared to be higher in bag cell neurons and the nearby abdominal ganglion than in the rest of the nervous system. In summary, the native current, which is involved in triggering reproduction, has characteristics consistent with the opening of a TRP-like non-selective cation channel. During the afterdischarge, DAG-mediated gating would be facilitated by PIP2 breakdown, while Ca2+ influx, presumably via the channel, would limit activation and prevent aberrant signalling.

P1-B-54: The AMPA receptor-GSG1L signaling complex is uniquely identified by its spatiotemporal expression, native interactome, and a privileged allosteric site

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Transmembrane AMPA receptor regulatory proteins (TARPs) and germ cell-specific gene 1-like protein (GSG1L) are AMPA receptor (AMPAR) auxiliary subunits that regulate glutamatergic synapse strength and plasticity. Although structurally similar claudin superfamily members, TARPs and GSG1L are referred to as opposing modulators of AMPAR function given their differential effects on gating and permeation. While AMPAR-TARP complexes have been extensively studied in both native and recombinant systems, far less is known about AMPAR-GSG1L complexes. Here, we use histology, proteomics, and electrophysiology to study the spatiotemporal expression, native interactome and functional properties of GSG1L. We show that although GSG1L is globally present at relatively low levels, its expression profile is cell-type specific and developmentally regulated. While it is established that TARPs modulate channel gating through the evolutionarily-conserved KGK site on the ligand-binding domain (LBD), we demonstrate that the primary effect of GSG1L is mediated via an exclusive allosteric site. Moreover, mutation of these regulatory sites reveals that the core AMPAR and auxiliary proteins coordinate via the GluA2 subunit to modify the time course of channel gating. Unlike TARPs, tethering GSG1L subunits to the AMPAR disrupts the canonical features associated with GSG1L, demonstrating that the structural basis underlying TARP and GSG1L modulation must be different. Together, our work identifies the AMPAR-GSG1L complex as an enigma amongst ion channels that uniquely shapes glutamatergic transmission.

P1-B-55: AMPA receptor gating unveils a hidden calcium pocket critical to ion transport

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α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA) subtype ionotropic glutamate receptors (iGluRs) are critical to synaptic transmission, plasticity, and learning. Canonically, divalent cation permeability of AMPARs is known to be determined by RNA-editing at the Q/R site in the pore region. However, understanding of the mechanism and structural basis remains unresolved. Here, we investigated the open-pore architecture of the calcium-permeable AMPAR (CP-AMPAR) in complex with auxiliary protein TARP γ2 under various ionic conditions at high resolution (2.3-2.6Å). Our results show that, different from dehydrated cations through potassium channels, numerous putative ion and water

densities are observed in the pore of AMPARs. Moreover, the conserved SYTANLAAF motif at the gate in iGluRs converts to a calcium binding site (site-G) in the open state. Functionally, the novel site-G is shown to be crucial for external calcium mediated channel block and calcium permeability. The seizure related N619K mutation adjacent to site-G promotes channel opening, but attenuates calcium binding, and therefore reduces external calcium block and calcium permeability. Identification of site-G extends the prevailing view on the mechanism of calcium permeability in AMPARs built upon the Q/R-site in the selectivity filter. Importantly, its conservation amongst iGluRs suggests a broader role in regulating monovalent versus divalent ion permeability.

P1-B-56: GluA2-containing AMPARs form a continuum of Ca2+ permeability

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AMPA receptors (AMPARs) are tetrameric glutamate-gated ion channels formed by GluA1-4 subunits. They mediate most of the fast excitatory synaptic transmission in the central nervous system (CNS) and are fundamental to brain function. AMPARs can be classified as GluA2-containing or GluA2-lacking, where the presence of GluA2 is assumed to dictate Ca2+ permeability and endogenous polyamine block. Here we show it is not the case. Specifically, we show how two abundant families of AMPAR auxiliary subunits, TARPs and CNIHs, fine-tune Ca2+ permeation of GluA2-containing AMPARs in a manner that has not been appreciated previously. Depending on the type (g2 or g8), number, and position, TARPs can differentially modulate Ca2+ permeability of GluA1/A2 and GluA2/A3 receptors, contrary to the conventional understanding. We also show that the addition of CNIHs to the AMPAR-TARP complex boosts Ca2+ permeability in specific subunit combinations. Furthermore, mutations in the pore region which affect ion permeation suggest that a trade-off exists between polyamine block and Ca2+ permeation: AMPARs insensitive to endogenous polyamines can exhibit a wide range of Ca2+ permeability depending on composition, while polyamine block only affects highly Ca2+ permeable AMPARs. Altogether, our data on recombinant and native AMPARs establishes a previously unappreciated continuum of Ca2+ permeability in GluA2-containing receptors, identifying a new family of AMPARs.

P1-B-58: Acetylcholine acts as a cell-type-specific switch for behavioral timescale activity

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Acetylcholine (ACh) plays an important role in the encoding of new memories. The subiculum, a brain region essential for memory, receives both intrahippocampal and ACh input while also serving as the primary output of the hippocampus. Transcriptomic work from our laboratory has illustrated the subiculum contains a diverse set of excitatory neuron subtypes, including a unique group of cells that occupy the deepest layer of the subiculum ("deep cells"). Importantly, our transcriptomic work also showed deep cells express specialized nicotinic and muscarinic ACh receptors. To investigate intrinsic differences between deep and classical pyramidal cells, we performed 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. Upon application of carbachol (CCh), an ACh nicotinic and muscarinic receptor agonist, we also found differential responses to both chronic and transient application of CCh. In particular, deep cells showed a sustained membrane depolarization and firing rate relative to classical pyramidal cells. In total, our results illustrate ACh reorganizes subicular activity in a cell-type-specific manner and can influence cellular dynamics on slow and behaviorally relevant timescales. As such, the subiculum may contain an ACh dependent microcircuit responsible for memory encoding.

P1-B-59: Effects of myelin distribution on axonal conduction

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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. Previous studies examining action potential propagation along myelinated axons are based on stereotyped cases under 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 to answer 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 a mathematical model and provide both computational and mathematical analysis. Our findings show that the generation of myelin early in development is an inaccurate process associated with aberrant ultrastructural features that require substantial refinement.

P1-B-60: Astrocytes derived from engrafted human neural precursor cells (NPCs) exhibit pro-regenerative phenotype in spinal cord injury

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Traumatic spinal cord injury (SCI) causes progressive neurodegeneration and disruption of spinal circuitry that leads to neurological deficits in young adults. Transplantation of neural precursor cells (NPC) is a promising approach to re-establish the damaged neuron-glia network that is essential for functional recovery after SCI. We recently reported that engrafted human NPCs can replace spinal cord neurons and

integrate within the spinal network. Interestingly, a higher population of NPC graft were also differentiated into astrocytes. In this study, we aimed to determine whether human NPC-derived astrocytes are phenotypically different than endogenous spinal astrocytes, particularly in matrix remodeling, inflammation and neurogenesis. Our in vitro experiments indicate that upon activation, NPC-derived astrocytes produce lower amount of chondroitin sulfate proteoglycans (CSPGs) compared to activated human spinal astrocytes, and have the capacity to digest CSPGs. Of note, CSPGs are upregulated in SCI and inhibit repair process. In co-culture system, activated spinal astrocytes significantly limit survival, growth and proliferation of NPCs, while activated NPC-derived astrocytes promoted neurogenesis and neuronal maturity of NPCs. In rat SCI, transplanted human NPC-derived astrocytes exhibit pro-regenerative phenotype compared to pro-inflammatory phenotype of engrafted human spinal astrocytes. Taken together, our study suggests that human NPC-derived astrocytes exhibit reparative phenotype in the injured spinal cord and facilitate neuronal replacement and graft integration.

P1-B-61: Dysfunctional somatodendritic AMPA receptor signaling in Fragile X Syndrome

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Fragile X syndrome (FXS) is the most common single-gene cause of inherited intellectual disability and autism. Affected individuals and preclinical mouse models show brain hyperexcitability, although the underlying mechanism is poorly understood. Here we show that loss of Fragile X Messenger Ribonucleoprotein (FMRP) alters dendritic signalling and excitability in cerebellar molecular layer interneurons (MLIs - stellate cells). We observed a large but briefer excitatory postsynaptic potential (EPSP) in Fmr1-/- stellate cells (SCs) following excitatory parallel fiber (PF) stimulation. We demonstrate that the change in EPSP halfwidth is caused by an increased GABAergic transmission. The enlarged peak amplitude in Fmr1-/- SCs is due to decreased surface expression of TEA-sensitive delayed rectifier potassium channel (Kdr) currents and a delay in their activation properties. Computational H-H modelling revealed that the dendritic Kdr is critical for EPSP amplitude and hyperexcitability. Pharmacological block by TEA converted the profile of EPSP in WT SCs to that of Fmr1-/- mice further validating the importance of Kdr channel. Interestingly, the introduction of an N-terminal fragment of FMRP into Fmr1-/- mice restore the EPSP amplitude and associated hyperexcitability to that of WT mice. Contrary to conventional understanding, our study demonstrates that neuronal signalling deficits in FXS can also include translational independent mechanisms that can be corrected acutely by using a fragment of FMRP.

P1-B-62: Delayed rectifier contribution to dendrosomatic signalling in inhibitory cerebellar interneurons

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Fragile X syndrome, the most common single gene cause of inherited intellectual disability, is associated with CNS hyperexcitability. Here we demonstrate that the loss of the protein product of the Fmr1 gene in mice alters dendritic signaling and excitability in cerebellar stellate cells (SC). In Fmr1 knockout (Fmr1-/-) mice, SCs have larger excitatory postsynaptic potentials (EPSP) following parallel fiber stimulation and have diminished levels of A-type and delayed rectifier potassium channel (Kdr) currents. Using an established 1-compartment Hodgkin-Huxley (HH) type model we find that attenuation in A-type, Kdr and calcium dependent potassium currents are unable to reproduce the experimentally observed increases in EPSPs. In an expanded 2-compartment HH type model we assess the relative contributions of somatic and dendritic ion currents in shaping SC EPSPs. From this 2-compartment model, we predict that the reduction of dendritic Kdr is the key determinant of EPSP amplitude. The involvement of Kdrs in increased Fmr1-/- SC EPSP amplitude was validated experimentally with increased EPSP amplitude in WT SCs after TEA block of Kdrs. A heterogeneous population of 1000 2-compartment SC models was generated by sampling model parameters from Gaussian distributions. The simulated firing within these models was increased after reduction of dendritic Kdr, demonstrating the role of dendritic Kdr in regulating SC excitability. Taken together, dendritic delayed rectifier modulation is key to disruption of dendrosomatic signalling and resulting hyperexcitability in Fmr1-/- SCs.

P1-B-64: Restoring synapse physiology through targeted degradation of PSD-95 in an autism model

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Autism is a neurodevelopmental disorder characterized by cognitive, social and behavioral impairments. A broad diversity of genetic and environmental factors lead to autism, many of which alter the development and function of synapses. MDGAs (MAM domain-containing glycosylphosphatidylinositol anchors) are synapse organizers that negatively regulate interactions between neurexins and neuroligins, which fall within a major autism pathway. Accordingly, mice lacking a single copy of MDGA2 (Mdga2+/-) demonstrate behaviors consistent with autism, along with upregulated glutamatergic synapses and PSD-95 family scaffolding proteins. Here, we are testing major forms of synaptic plasticity (long-term potentiation, long-term depression) and whether targeted reversal of exaggerated PSD-95 expression restores plasticity to wild-type levels. Additionally, we have probed for these changes across the dorsal-ventral axis of the hippocampus, to determine the effects of MDGA2 reduction in regions associated with social (ventral) and contextual (dorsal) cognition, which are both impaired in Mdga2+/-mice. This project has implications for targeted therapeutics in humans, setting the stage for restoring synapses and reducing symptom severity for those with autism and other disorders characterized by impaired synapses.

P1-B-65: 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 the neurotransmitter 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. Altered Cl- homeostasis is associated with various neurological disorders including autism spectrum disorder (ASD). KCC2 protein expression and/or function can be regulated by its interactome. I am investigating strategies to promote KCC2 function by manipulating its novel interacting partners, namely PACSIN1, SNAP-25, and 14-3-3. SNAP-25 is a part of the SNARE protein complex and 14-3-3 proteins are a family of phospho-binding proteins. I found that SNAP-25 knockdown and 14-3-3 (ε and γ isoforms) overexpression resulted in reduced KCC2 expression in primary neurons. I am currently examining mechanisms underlying the regulation of KCC2 by these interacting partners. Parallelly, we developed peptide-based protein-protein interaction (PPI) inhibitors that prevent KCC2-PACSIN1 interaction. PACSIN1 is a neuron-specific negative regulator of KCC2, involved in clathrin-mediated endocytosis. Therefore, inhibiting KCC2-PACSIN1 interaction using PPI inhibitors can provide a neuron-specific therapeutic strategy to rescue KCC2. I have identified and validated two PPI inhibitors that increase total KCC2 expression and hyperpolarize EGABA in primary neurons indicating enhanced KCC2 function. I am currently working on the optimization of these PPI inhibitors for in-vivo use.

P1-B-66: Mistrafficking of KCC2 in Endolysosomal system in the hippocampus of Christianson Syndrome mouse 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 located in recycling endosomes we investigated if loss of NHE6 resulted in low levels and or mistrafficking of KCC2 to overacidification of endosomes which could lead to autism and epilepsy in CS patients. Using immunoblotting in a murine model of CS (NHE6KO) we found that KCC2 levels were significantly lower in the hippocampi of KO vs WT at PND 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 acute hippocampal slices of P60 tissue 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 suggesting 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.

P1-B-67: Asymmetrical distribution of excitatory N-methyl-D-aspartate receptor subunits across the mediolateral axis of the rodent and human superficial dorsal horn.

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Despite chronic pain being highly prevalent, there are limited treatments that are both safe and effective. N-methyl-D-aspartate receptors (NMDARs) are glutamatergic receptors found across the central nervous system, with GluN2 subunit variants in the spinal cord consisting of GluN2A, GluN2B, and GluN2D. The superficial dorsal horn (SDH) is a critical site for nociceptive signalling, and NMDARs are essential regulators of plasticity and excitability within SDH pain processing circuits. However, the relative expression and localization of GluN2 NMDAR subunits within the SDH across sex and species remains unknown. To investigate GluN2 subunit localization across the dorsal horn, we used immunohistochemistry techniques on rat and human lumbar and thoracic spinal cord tissue for both sexes, in conjunction with antigen retrieval and tyramide signal amplification. We found that GluN2 subunits are preferentially expressed in the SDH of rat and human spinal cord tissue in both sexes. However, there is a heightened localization of GluN2 subunits to the lateral lumbar SDH of rats compared to a uniform GluN2 distribution across the mediolateral SDH axis for human thoracic and lumbar segments. We are currently investigating whether this divergence is due to sampling from different spinal segments or is driven by a species difference. Moreover, we are co-staining with neuronal (NeuN) and presynaptic afferent (CGRP) markers to test whether the GluN2 asymmetry in rodents is specific to differences in NMDAR distribution and not cellular density or synaptic innervation. These findings highlight potential differential NMDAR signalling across the mediolateral SDH somatotopic map, which may differ across species.

P1-B-68: Nociceptor activity induces non-ionotropic NMDA receptor signaling to enable spinal reconsolidation and reverse pathological pain

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Chronic, pathological pain is a highly debilitating condition that can arise and be maintained through central sensitization. Central sensitization shares mechanistic and phenotypic parallels with memory formation. In a sensory model of memory reconsolidation, plastic changes underlying pain hypersensitivity can be dynamically regulated and reversed following the reactivation of sensitized sensory pathways. However, the mechanisms by which synaptic reactivation induces destabilization of the spinal 'pain engram' are unclear. We identified non-ionotropic NMDA receptor (NI-NMDAR) signaling as necessary and sufficient for the reactive destabilization of dorsal horn long-term potentiation (LTP) and the reversal of mechanical sensitization associated with central sensitization. NI-NMDA signaling

engaged directly or through the reactivation of sensitized sensory networks was associated with the degradation of excitatory postsynaptic proteins. Our findings reveal a unique signaling pathway that may be exploited to treat underlying causes of chronic pain and present a novel mechanism by which engrams are destabilized in reconsolidation.

P1-B-69: Tanycytes in sensory circumventricular organs

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Tanycytes are specialized glial cells found in regions of the brain with an incomplete blood-brain barrier due to the presence of fenestrated vasculature. These regions, called circumventricular organs (CVOs), are key areas found at the interface of the brain and the peripheral circulation. Tanycytes have a unique morphology: Cell bodies contacting the cerebral spinal fluid and long processes extending into the brain parenchyma. The Organum Vasculosum of the Lamina Terminalis (OVLT) and the Subfornical Organ (SFO) are sensory CVOs containing neurons activated by increases in blood osmolality and Na+, involved in regulating hydromineral balance and cardiovascular function. We found that OVLT and SFO tanycytes feature numerous small protrusions along their processes, and these processes branch to contact both fenestrated blood vessels and neuronal cell bodies. We hypothesize that tanycytes in these sensory CVOs can sense changes in the composition of peripheral circulation and communicate to local neurons, modulating their activity. To determine the signals sensed by OVLT and SFO tanycytes, we imaged intracellular Ca2+ levels with GCaMP6f. We found that OVLT and SFO tanycytes are activated by increases in extracellular Na+ and ATP. In addition, our results show that tanycytes in sensory CVOs express components of purinergic and glutamatergic signaling. Our findings imply that bidirectional communication between tanycytes and neurons in the sensory CVOs is mediated by glutamate release and purinergic signaling, and is modulated in response to changes in hydromineral balance.

P1-B-70: Microglia-mediated pruning of astrocytes increases vasopressin-releasing neuron activity in high salt diet

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High dietary salt increases arterial pressure partly through activation of magnocellular neurosecretory cells that secrete the 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 cause 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.

P1-B-71: Assessing sex differences in the effects of amyloid beta protein on excitatory synaptic responses in the lateral entorhinal cortex in vitro

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There are marked sex differences in the incidence of Alzheimer's disease (AD), with two-thirds of cases occurring in women, and rates rising drastically following menopause. This suggests a powerful role for ovarian hormones in women's risk for developing AD. The entorhinal cortex is a site of early neurodegeneration in AD, and the accumulation of soluble amyloid beta protein (Aβ) early in AD may promote hyperexcitability by enhancing the activation of NMDA glutamate receptors. We have previously investigated the role of amyloid beta (Aβ) in increasing excitatory transmission in the medial entorhinal cortex using recordings of field excitatory postsynaptic potentials (fEPSP) from brain slices obtained from male Long-Evans rats (7-10 wk-old). We found that 1 to 3 hour exposure to 100 µM Aβ1-42 significantly increased fEPSP amplitude compared to a control group. This effect was blocked by the NMDA receptor blocker D-AP5, indicating that NMDA receptors mediated the effects of Aβ. In the present study we investigated possible sex-differences in this LTP-like effect in the lateral entorhinal cortex of male and intact female rats. Preliminary results, however, showed no significant changes in fEPSP amplitude following incubation in Aβ in slices obtained from either male or female rats. Results may be due to differences in the susceptibility of the medial vs lateral entorhinal cortex to the effects of Aβ, or to differences in tissue preparation. Future experiments will also examine how co-incubation with 17β-estradiol may moderate the effects of Aβ on synaptic potentials.

P1-B-72: Cortico-tegmental pathway dynamics and its reshaping after chronic stress.

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Cortically driven dysregulation of subcortical circuits can trigger depressive-like behaviours in humans and animals. Recent findings from our lab showed that chronic variable stress (CVS) induces functional and morphological changes to cortical neurons projecting to the ventral tegmental area (VTA) in a sex-dependent fashion. However, whether these modifications could affect the synaptic transmission to downstream regions remain unclear. Using a trans-sectional viral strategy, we differentially identified downstream VTA neurons based on their connectivity with the medial prefrontal cortex (mPFC): we report the existence of a preponderant population that sends projections to the PFC and receives cortical feedback connections. Functionally, the optogenetic stimulation of ChR2-expressing cortical axons in live VTA slices revealed a short-term potentiation of glutamatergic transmission to connected cells, which was significantly impaired by 21 days of CVS in both male and female mice. Using a pharmacological approach, we discovered that this facilitation is mainly supported by presynaptic Ca2+-interacting proteins. Here, we characterized a novel form of Ca2+-dependent presynaptic plasticity at mPFC-VTA synapses, likely involved in emotional processing in male and female mice. Chronic stress induces a profound reorganization of the cortico-tegmental pathway, leading to maladaptive plasticity mechanisms

and impaired behavioral response. Understanding these effects will provide novel insights into the neuronal mechanisms underlying behavioral adaptations to chronic stress.

P1-C-73: Investigating the role of IRE1 in brain regeneration using a larval zebrafish model

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Stimulating humans' endogenous neural stem cells (NSCs) to regenerate neurons may be a viable therapy for traumatic brain injury (TBI). However, the cellular responses controlling NSCs post-TBI are unclear. Since it can regenerate neuronal tissue, the zebrafish is an excellent model to study the cell responses governing NSCs post-TBI. The Unfolded Protein Response (UPR) is a vertebrate conserved stress response. One of the proteins that controls the UPR is inositol requiring enzyme 1 (IRE1). IRE1 plays a key role in the responses of mammalian astrocytes and neurons post-TBI, but the role of IRE1 in NSCs remains unknown. The objective of this study is to characterize the role of IRE1 in NSCs post-TBI using a larval zebrafish model. We hypothesize that IRE1 activity increases post-TBI and is required for successful NSC-driven regeneration. Transgenic reporter fish that express GFP fluorescence upon IRE1 activation (xbp1s:eGFP) will be given a mechanical TBI in the dorsal forebrain at 5 days post-fertilization. Injured larvae will be bathed in EdU (proliferative marker) before sacrifice for immunohistochemical analysis. Brain tissue will be examined for an increase in IRE1 activity (GFP signal), and labeled with EdU and NSC markers (GFAP, Sox2) to determine if IRE1 activity increases in proliferating NSCs post-TBI. Preliminary data suggests that IRE1 activation increases by 1-day post-TBI with ongoing experiments assessing NSC markers. The results of this study will offer novel insight to the role of IRE1 in NSCs and potential future therapies for those suffering from TBI.

P1-C-74: Body-to-brain communication by the peripheral extracellular vesicles.

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Extracellular vesicles (EVs) are produced by all cell types. EVs play an important role in intercellular communications by transferring their functional cargo to recipient cells. Interestingly, their cargo depends on the physiopathological state of the donor cell. Peripheral EVs (pEVs), released by different organs, can propagate their cargos through the blood circulation. However, the role of pEVs in the communication between the periphery and the brain remains to be clarified. We hypothesized that pEVs pass through the blood-brain barrier (BBB) and then diffuse in the brain. For this, pEVs from human serum were enriched, characterized, and then labelled with a fluorescent probe. The diffusion of pEVs through the BBB was first studied on the bEnd3 endothelial cells using an in vitro Transwell model. Then, labeled pEVs were microinjected into the blood circulation of 2-days post-fertilization transgenic Danio rerio. The biodistribution of pEVs into larvae was monitored 1h and 24h post-injection by confocal microscopy. By using the Tg(flk1:EGFP) line, we observed the passage of the pEVs into the brain and their increased diffusion into the cerebral areas through the time. The important colocalization of pEVs with

endothelial cells suggest that these vesicles notably reach the brain through the BBB. Moreover with the Tg(huc:EGFP) and Tg(gfap:EGFP) lines, we demonstrated that pEVs were engulfed by neurons and glial cells, respectively. These results support our hypothesis and bring up new knowledge about the fate of pEVs after their passage through the brain barriers.

P1-C-75: Characterizing Von Economo Neurons in Schizophrenia and Major Depressive Disorder

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Von Economo neurons (VENs) are a type of bipolar spindle-shaped neurons found in some regions of the human brain, including the anterior cingulate cortex (ACC; layer V) and frontal insula (FI). These neurons, absent in rodents, have been described in a few other species with large brains and complex social structures, and been associated with guilt, embarrassment, trust, empathy and formation of social bonds, among others. Studies are increasingly implicating VENs in brain disorders: an alteration in the number and morphology of VENs has been reported in alcoholism, autism spectrum disorder (ASD), schizophrenia (SCZ), behavioral variant frontotemporal dementia (bvFTD) and suicide in psychosis. Recently, a transcriptomic analysis of VENs enabled the identification of differentially expressed genes in VENs vs pyramidal neurons, in particular a higher expression of genes associated with psychiatric and neurological disorders, including SCZ and depression. However, the implication of VENs in neuropsychiatric disorders remains to be largely characterized. With this project, we aim to identify the specific VEN features associated with major depressive disorder (MDD) and SCZ. I hypothesize that VEN densities, morphologies, and transcriptomic profiles display illness-specific alterations. Quantifications of VEN densities from post-mortem FI and ACC samples will be presented and compared with the densities of adjacent pyramidal cells. These results should provide a better understanding of the cerebral changes that occur in MDD and SCZ and shed new light on the possible implication of VENs in mental illness.

P1-C-76: Neurogliaform cell synaptic transmission and GABAergic signaling alteration in the hippocampal circuit of animal model of Rett syndrome

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Rett syndrome is a neurodevelopmental disorder caused by a mutation in the X-linked methyl-CpG-binding protein 2 gene (MeCP2). Rett syndrome patients have severe deficits in learning and memory, which result from alterations in hippocampal network connectivity and synaptic plasticity. Alterations in excitatory glutamatergic synaptic plasticity in the CA1 region of the hippocampus have been particularly well characterized in animal models of Rett syndrome, however, the mechanisms underlying this impaired excitatory plasticity are still not fully understood. In particular, the role that inhibitory GABAergic synaptic transmission plays in impaired excitatory plasticity is rudimentary, despite the growing evidence for the role of inhibition in learning and memory. We discovered that in Mecp2 −/Y

male mice, excitatory short-term plasticity is increased in CA1 pyramidal neurons, and this increase is dependent upon GABAergic inhibition. To determine how inhibition gates increased excitatory short-term plasticity, we examined the role of neurogliaform (NGF) interneurons, the most abundant dendrite-targeting interneuron subtype in the hippocampus. We found that NGF cells of Mecp2 −/Y male mice increased intrinsic excitability, decreased excitatory input, and have a reduction in the reversal potential for GABA due to a decrease in expression of the K -Cl- cotransporter, KCC2. Thus, dysregulated inhibition underlies altered excitatory short-term synaptic plasticity, which is known to underlie the deficits in learning and memory that characterize Rett syndrome.

P1-C-77: Can cannabis extracts treat brain system dysfunction and resultant memory impairments associated with Alzheimer's disease (AD) using a transgenic mouse model?

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Alzheimer's Disease (AD) is the most common age-related neurodegenerative disorder and is categorized by progressive memory loss and sweeping deterioration of one's cognitive ability. Amyloid beta (Aβ) protein accumulates in the brain during the progression of AD and is present in all forms, making it a protein of interest. Aβ accumulation creates prolonged inflammation in the brain leading to damage and further dysregulation. By targeting both Aβ and resultant inflammation, disease progression may be delayed. Cannabis is a naturally occurring plant that contains over 400 unique compounds, the two most researched are THC and CBD. In vivo studies show that at low doses, THC helps facilitate learning and memory and at high doses, CBD produces anti-inflammatory effects, and when used in combination they are far more effective. These cannabinoids are a promising treatment option for AD, as they target receptors located in the brain's memory centers (primarily, the hippocampus) and in the immune system. This project utilizes a daily oral dose of a low THC/high CBD extract to treat Aβ-related AD pathology in an Aβ precursor protein mouse model. A battery of memory-based behaviour tests (namely, the Morris Water Task and Novel Object Recognition Task) are used to evaluate brain system dysfunction. Using various immunohistochemical stains, Aβ and inflammatory markers are quantified to assess disease progression and severity. Overall, our findings should show that a combination extract will help improve brain system dysregulation and resultant memory impairments associated with AD.

P1-C-78: The ginger extract improves learning and memory impairment via gut-brain axis regulation in a rat Alzheimer's disease-like model

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Background: Alzheimer's disease (AD) is the most prevalent form of dementia with multiple causes and no effective treatment. Recently, it is suggested that there is a link between AD progress and gut

microbiota activity. Ginger is a plant with anti-inflammatory, antioxidant, and neuroprotective effects and has recently been considered by researchers as a potential treatment to reduce AD symptoms. Methods: In this study, using ovariectomy and Digalactose injection, a model of AD was induced in female rats, and then the protective effects of oral administration of ginger ethanolic extract were investigated. Y-maze, Barnes maze and shuttle box tests were done to assess the animals' learning and memory. Using GC-mass chromatography, ELISA, Immunohistochemistry and tissue staining techniques Changes in the amount of short-chain fatty acids (SCFAs), plasma and hippocampus neuroinflammatory markers and histological changes in the intestine and hippocampus were assessed in sham, disease and treatment groups. Results: Oral administration of ginger ethanolic extract could improve the gut microbiota activity and increase the amount of SCFAs in fecal samples and intestinal tight junction proteins. Moreover, ginger extract attenuated TNF-α And IL-1β concentration in the hippocampus and plasma. Also, cell death and Amyloid plaques notably decreased in the ginger-treated hippocampal tissue. All these physiological changes led to better performance in behavioral tasks in the rats treated with ginger in comparison to the disease group. Conclusion: These findings provide evidence for the positive effects of ginger on the gut-brain axis followed by improvement in learning and memory via a reduction in neuroinflammation.

P1-C-79: Single-nucleus chromatin accessibility and transcriptomic mosaicism in C9orf72-linked amyotrophic lateral sclerosis and frontotemporal lobar degeneration

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The contributions of individual cell types to the pathogenic mechanisms causing amyotrophic lateral sclerosis (ALS) and the related disease, frontotemporal lobar degeneration (FTLD) are poorly understood. Here, we have generated a single nucleus transcriptomic and open chromatin atlas of 205,487 cells from orbitofrontal cortex of ALS cases that carry hexanucleotide repeat expansions in C9orf72 (C9), the most frequent genetic cause of disease. We identify candidate cell subtype-specific transcription factor (TF) motifs and cis-regulatory elements underlying disease related gene expression changes. C9-ALS/FTLD microglia showed a shift towards a disease associated cell state as exemplified by differential peak accessibility of SPP1 with concomitant transcript upregulation. We interrogated cell type-specific alternative polyadenylation, identifying widespread 3'UTR lengthening of transcripts with enrichment for C9-ALS/FLTD-associated TF motifs in distal peaks. These 3'UTR changes were particularly evident in excitatory neurons, where the corresponding TFs were downregulated. These findings significantly advance our understanding of the single cell transcriptomic and epigenomic landscape underlying C9-ALS/FTLD and ALS without FTLD and provides a timely resource for further molecular interrogation.

P1-C-80: A dynamic balance between neuronal death and clearance after acute brain injury

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After acute brain injury, neuronal apoptosis may overwhelm the capacity for microglial phagocytosis, creating a queue of dying neurons awaiting clearance. The size of this queue should be equally sensitive to changes in neuronal death and the rate of phagocytosis, and thus a dynamic balance between death and clearance should exist. We evaluated the death of neurons in a chronically epileptic in vitro preparation in which serial multiphoton microscopy could be performed over a period of days or weeks. Organotypic hippocampal slice cultures were made from mice on P6 and incubated in vitro. Slices were imaged with transgenic fluorophores to assess healthy neurons, and various bath-applied fluorophores to assess apoptotic neurons. Serial imaging demonstrated that the capacity for microglial phagocytosis of dying neurons was overwhelmed for two weeks, based on an accumulation of neurons which stained positive for cell death markers such as propidium iodide. Altering phagocytosis rates, for example by poisoning the microglia with liposomal clodronate, dramatically changed the number of visibly dying neurons. Similar effects were generated when the visibility of dying neurons was altered by changing the membrane permeability for vital stains. Canonically neuroprotective interventions such as seizure blockade with kynurenate and neurotoxic maneuvers such as perinatal ethanol exposure were mediated by effects on microglial activity and the membrane permeability of apoptotic neurons, and had either no or opposing effects on healthy surviving neurons.

P1-C-81: Antagonism of the muscarinic acetylcholine type 1 receptor activates TRPM3 to augment mitochondrial function and drive sensory neuron regeneration

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Diabetic peripheral neuropathy (DPN) comprises a dying-back axonal degeneration leading to sensory loss and neuropathic pain. We are developing strategies to drive regeneration of sensory neurons by blocking the muscarinic acetylcholine type 1 receptor (M1R). M1R antagonism induces a slow increase of intracellular Ca2+ that stimulates mitochondrial function and neurite outgrowth. The transient receptor potential channel 3 (TRPM3) is a potential source of Ca2+ when phosphatidylinositol 4,5-bisphosphate (PIP2) levels are low. Hence, we hypothesized that M1R antagonism caused blockade of G protein signaling leading to PIP2 levels rising and activation of TRPM3. Adult dorsal root ganglion (DRG) sensory neurons derived from control or type 1 diabetic rats were used to test this hypothesis. TRPM3 agonists elevated mitochondrial function and augmented neurite outgrowth and this effect was abolished by TRPM3 inhibitors blocking Ca2+ influx. Moreover, shRNA-mediated TRPM3 knockdown blocked TRPM3 agonist stimulation. Pirenzepine, a selective M1R antagonist, induced neurite outgrowth which was suppressed by TRPM3 knockdown. Untargeted metabolomics revealed a marked increase in galactose and pyruvate metabolism induced by TRPM3 agonists, demonstrating TRPM3 activation stimulated neuronal bioenergetics. These novel results reveal that TRPM3 channels mediate the stimulatory effect of M1R antagonism on mitochondrial function and neurite growth. These findings support ongoing

clinical trials with M1R antagonists in persons with peripheral neuropathies and DPN. Funded by CIHR # PJT-162172.

P1-C-82: Brain distribution of metabotropic glutamate 2 receptor in hemi-parkinsonian rats with L-DOPA-induced dyskinesia

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Objective: To determine the distribution of metabotropic glutamate 2 (mGlu2) receptors in the basal ganglia in 6-hydroxydopamine (6-OHDA)-lesioned rats with L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesia. Background: L-DOPA-induced dyskinesia affects nearly 90% of Parkinson's disease patients after years of treatment with L-DOPA. We have previously shown that mGlu2 stimulation reduces dyskinesia in the rat and marmoset models of PD. Here, we seek to determine which brain areas might mediate this anti-dyskinetic effect. Methods: Hemi-parkinsonism was induced by 6-OHDA injection. Parkinsonism was determined using the cylinder test, while dyskinesia was measured with the abnormal involuntary movements scale. Four different groups of rats were created: dyskinetic and non-dyskinetic L-DOPA-treated 6-OHDA rats, L-DOPA-naïve 6-OHDA rats, and sham-lesioned rats. MGlu2 receptors were quantified in the motor cortex (M1), striatum, globus pallidus (GP), entopeduncular nucleus (EP), subthalamic nucleus (STN), substantia nigra (SN), and ventral lateral (VL) nucleus of the thalamus by autoradiographic binding with [3H]-LY-341,495 and L-glutamic acid as the cold ligand. Results: In the ipsilateral hemisphere, non-dyskinetic rats exhibited a decrease in [3H]-LY-341,495 binding in the GP (28% vs sham-lesioned, $P < 0.05$; 23% vs L-DOPA-naïve, $P < 0.001$), and a decrease in M1 (49% vs sham-lesioned, $P < 0.05$; 45% vs L-DOPA-naïve, $P < 0.001$). Dyskinetic rats showed an increase in binding in M1 (43% vs non-dyskinetic, $P < 0.05$). Conclusion: The results indicate L-DOPA treatment may alter mGlu2 expression in specific brain regions, suggesting that mGlu2 receptors may be part of an endogenous compensatory mechanism to reduce dyskinesia.

P1-C-83: The Role of Bdnf Pathway in Energy Homeostasis Deficit in Smith-Magenis syndrome Mice

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Severe hyperphagia, metabolic defect, and obesity are debilitating features of Smith-Magenis syndrome (SMS), a monogenetic disorder caused by haploinsufficiency of retinoic acid induced 1 (RAI1). Rai1 regulates the transcription of many neurodevelopmental genes including Bdnf. Bdnf is a secreted molecule which regulates energy metabolism through binding to its downstream receptor TrkB. Bdnf is downregulated in the hypothalamus of SMS mice. This observation led us to further analyze the contribution of Bdnf signalling in SMS pathology and therapeutically targeting the Bdnf pathway. We first performed reverse phase protein analyses (RPPA) to show that multiple Bdnf downstream targets were downregulated in SMS mice. We next deciphered the function of Rai1 in a discrete set of Bdnf-producing

cells, which regulates energy homeostasis through multiple hypothalamic cell types including neurons residing in the paraventricular nucleus of hypothalamus (PVH). We generated Rai1 conditional knock out (cKO) model (Rai1-deletion in Bdnf producing neurons) and demonstrated that loss of Rai1 from Bdnf-producing cells contributes to obesity in SMS by selective altering fat deposition in several organs. Furthermore, 3-weeks old cKO mice also showed reduced neuronal excitability in the PVH. We further found that selective deletion of Rai1 from the Bdnf neurons in PVH Next, we explored the therapeutic potential of targeting Bdnf downstream signalling by using LM22A-4 (a TrkB partial agonist). Our results demonstrate that LM22A-4 treatment significantly reduces the body weight in SMS mice and delays the onset of obesity. Our work shows the pathological contribution of Bdnf pathways in SMS and demonstrate that targeting Bdnf signaling has a potential to ameliorate SMS symtptoms.

P1-C-84: Transcriptomic organization of the human brain in symptomatic profile of depression

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OBJECTIVE - Major depressive disorder (MDD) is a highly pervasive and recurrent disease. Despite its significant burden on modern societies, current strategies to threat the disease remain relatively inefficient. This incapacity to appropriately threat MDD likely results from the heterogeneity in its symptomatic profile. While these symptoms are broadly different in many dimensions, including their underlying biological substrate and associated molecular mechanisms, their associations with the activity of distinct transcriptional signatures in the human brain are still unknown. In this study, we aimed to identify transcriptional signatures associated with the expression of specific symptomatic profiles across brain regions in males and females with MDD, employing a data-driven system-based approach. METHODS - We used the RNA extracted from 89 post-mortem brain samples across six brain regions in men and women with and without MDD along with patients' symptomatic descriptions. We utilized weighted gene co-expression network analysis to create gene networks most pertinent to the expression of symptomatic features of depression. RESULTS - Our analysis identified gene networks the most importantly associated with the expression of each respective symptom of MDD, in men and women. For instance, we found a GABAergic gene network in the OFC, the most relevant construction, associated with the expression of insomnia/hypersomnia in men. CONCLUSION - Our findings suggest that the expression of specific symptoms of MDD can be associated with the activity of gene networks in distinct brain regions of men and women. This provides novel information on the molecular mechanisms underlying the functional changes observed in the brain.

P1-C-85: MicroRNA-146b decreases inflammatory responses in human and rodent-derived astrocytes and provides insights into the neuroimmunological mechanisms in multiple sclerosis

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MicroRNAs (miRNAs) are small nucleic acid sequences that interfere with protein translation via binding with targeted mRNAs to prevent translation. In multiple sclerosis (MS), an immune-mediated

demyelinating disease of the CNS, miRNA expression within both the neural and immune compartments are dysregulated. Mir-146b is a miRNA that inhibits translation of TRAF6, an activator protein of NF-kB. In MS, mir-146b is increased in blood samples, thus indicating its potential pathologic relevance to MS. The NLRP3 inflammasome is a protein complex activated in MS inflammation that produces inflammatory cytokines and chemokines. Activation of the NLRP3 inflammasome occurs through toll-like receptor 4 (TLR4) activation. Since TRAF6 is also activated by the TLR4 pathway, we hypothesize that upregulation of mir-146b may function as a rescue mechanism to minimize NLRP3 activation, thereby positively impacting oligodendrocyte progenitor cell development via indirect activation of glial cells. In primary murine and human astrocytes transfected with mir-146b mimic and exposed to IL-1β, our results demonstrate that mir-146b decreases astrocytic production of IL-6, an indicator of astrocytic activity. Future experiments will observe a role for mir-146b on oligodendrocytes differentiation in the presence of astrocytes, as well as a role of mir-146b during NLRP3 activation. In summary, mir-146b may modulate the neuroimmune response in MS, and serve as a potential and accessible MS biomarker in clinical settings.

P1-C-86: Regulation of the intracellular accumulation of Tau by Numb and its role in tauopathies

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Tauopathies are a large family of neurodegenerative diseases which includes Alzheimer's disease (AD) and are characterized by dysregulation of the microtubule binding protein Tau, which becomes hyperphosphorylated, resulting in elevated intracellular levels of Tau and formation of aggregates called neurofibrillary tangles. These tangles are known to be toxic to neurons, and therefore understanding how Tau is regulated in health and disease is an important step in better understanding the pathogenesis of tauopathies. Recently, our lab has shown that the long isoform of a well-known endocytic adaptor protein, Numb72, functions as a negative regulator of intracellular Tau levels (Lacomme et al., Sci. Adv., 2022). We found that overexpressing Numb72 in retinal neurons of mouse models of AD and tauopathy significantly reduces Tau accumulation and increases neuronal survival, but whether Numb72 can also function as a neuroprotective agent in neurons outside of the retina remains unknown. To address this question, we generated a new transgenic mouse line that expresses Numb72 in a Cre-dependent manner, allowing us to elevate the levels of Numb72 in various regions of the brain. We hypothesize that overexpression of Numb72 will generally reduce intraneuronal accumulation of Tau and prevent degeneration of hippocampal neurons in tauopathy mouse models, thereby reducing the progression of learning and memory deficits. Overall, this project will help contribute to the development of Numb72 as a novel therapeutic target for tauopathies.

P1-C-87: Acute effects of pubertal gut dysbiosis on the cellular mechanisms associated with neurodegeneration in male and female CD-1 mice

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Gut dysbiosis during puberty has enduring effects on immune responsivity and may play a role in the development of various pathologies such as Alzheimer's and Parkinson's disease. However, the mechanisms underlying the effects of gut dysbiosis on the cellular mechanisms related to neurodegeneration remain unclear. Therefore, the current study was designed to examine the acute effects of pubertal antimicrobial and lipopolysaccharide (LPS) treatments on the cellular mechanisms associated with neurodegenerative disorders in male and female mice. A total of 56 (28 male and 28 female) CD-1 mice were used in this experiment. At five weeks of age, male and female mice were treated with either a combination of antimicrobial agents or water, twice a day, for seven days. At six weeks of age, the mice received an intraperitoneal injection of LPS or saline. Eight hours following the injection, mice were euthanized and brains and intestinal samples were collected. The caudate-putamen (CP), substansia nigra (SN), and ileum were extracted and processed with western blot to examine complement 3 (C3) and tyrosine hydroxylase (TH) protein expression in the brain along with occludin protein expression in the ileum. The results indicated that LPS-treated males displayed significantly less C3 expression in the SN while LPS-treated females displayed significantly greater occludin expression in the ileum. Overall, these findings suggest that pubertal female mice may have a more adaptive response to LPS and antimicrobial treatment in comparison to pubertal male mice.

P1-C-88: Progressive Emergence of Striatal Synaptic Alterations in Glutamate

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The autosomal dominant D620N mutation in Vacuolar Protein Sorting 35 (VPS35) causes a clinically-typical form of late-onset PD. Canonically, VPS35 functions as a core subunit of the retromer complex that recycles transmembrane cargo from sorting endosomes. Despite its link to neurodegenerative disorders, little is known about VPS35 function in neurons. We report that primary neuron cultures from D620N knock-in mice show increased surface expression of GluA1 AMPA-type glutamate receptors and increased glutamate synaptic transmission at 3 weeks in vitro. To study this in situ, we conducted brain slice experiments from knock-in mice at 1, 3, & 6 months of age. Interestingly, striatal glutamate transmission is similar to littermate controls at 1 month. By 6 months, glutamate transmission is increased in knock-in striata as evidenced by changes in spontaneous, and electrically- and optogenetically- evoked glutamate transmission measurements. Glutamate release was further assayed using the fluorescent glutamate sensor, iGluSnFR, and was also found to be increased in knock-in animals at 6 months relative to their littermate controls. This emergent synaptic dysfunction in striatal glutamate transmission may relate to non-motor aspects of the disease or perhaps even contribute to pathogenicity. Our hope is that this information furthers the understanding of the mechanism by which individuals carrying mutations in VPS35 develop PD. This will aid in the pursuit of new avenues for therapy, neuroprotection, and ultimately, a cure for PD.

P1-C-89: Probing the nature of changes in synaptic transmission associated with APOE variant-mediated resistance or predisposition to Alzheimer's disease

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Alzheimer's Disease (AD) is a progressive neurodegenerative disorder, characterized by cognitive impairments, including memory loss. Variants in Apolipoprotein E (APOE), a cholesterol carrier involved with lipid transport and injury repair in the brain, are predictive of resilience to or predilection for AD. There are 3 APOE gene polymorphic alleles (E2, E3, E4). Interestingly, E2 may be neuroprotective whereas the E4 allele is found in ~40% of those with AD. Consistent with humans, mice expressing E4 (APOE4-Knock-in; KI) demonstrate hallmarks of AD including increased amyloid-β load, neurodegeneration, memory impairment and altered synaptic plasticity. However, a combination of conflicting results and a paucity of data examining alternative mechanisms raises the question: What is the nature of synaptic plasticity changes in mice harboring E4? To address this, we used a cellular analog of memory known as long-term potentiation (LTP), focusing on how quickly it decays as a proxy for accelerated memory loss. Surprisingly, LTP decayed faster in APOE3-KI mice when compared to APOE4- or APOE2-KI mice. To further probe the locus of synaptic changes, we assayed a form of short-term plasticity that requires recruitment of the reserve pool of synaptic vesicles. Interestingly, APOE2 synaptic responses decayed more rapidly, consistent with a faster depletion rate of reserve vesicles. Our results suggest that APOE2 confers resistance to AD through enhanced recruitment of the reserve pool of synaptic vesicles which may boost synaptic transmission during sustained neural activity.

P1-C-90: Sexual dimorphisms in neuronal systems function and behaviour in a model system of autism spectrum disorders

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Autism Spectrum Disorders (ASD) exhibit prominent sexual dimorphisms in age of onset, prevalence, etiology and presentation. This study therefore aimed to provide essential information on sex differences in a model widely used to study idiopathic ASD, the valproic acid (VPA) model. To evaluate sex differences in behaviour, adolescent male and female VPA and control rats underwent testing in the three-chamber social test, novel object recognition, object location and elevated plus maze. Following this, rats were implanted with electrodes into the prefrontal cortex (PFC), anterior cingulate cortex (Cg) and dorsal hippocampus (HIP) and spontaneous local field potential recordings were taken from freely moving animals. VPA-exposed female rats displayed greater anxiety compared to sex-matched controls, deficits in recognition memory, and reduced social index scores although they were more sociable than male VPA rats. VPA males showed difficulties in location memory and had a lower social index score compared to male controls. Sex differences in oscillatory activity were also evident. Female VPA rats had elevated delta power, and lower theta power in the PFC, whereas male VPA rats exhibited high frequency alterations, with elevated beta and high gamma power in the Cg, and lower Cg-HIP coherence. These findings show that there are prominent differences in behaviour and neuronal function in male and female VPA rats that may have relevance to the sexual dimorphisms observed in human ASD.

P1-C-91: Examining the influence of child abuse on the relation between perineuronal nets and myelination of parvalbumin interneurons in the human prefrontal cortex of depressed suicides

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Parvalbumin interneuron (PV) maturation in the neocortex is associated with the opening of developmental critical periods (CP). During CP, brain circuits are more easily altered by the external environment. Perineuronal net (PNN) maturation around PV cells is associated with the closing of these CP. Recent reports highlight that cortical PV axons are myelinated, and that myelination also plays a role in ending CP. Our lab recently reported that a history of child abuse (CA), a risk factor for depression and suicide, is associated with increased PNNs in the ventromedial prefrontal cortex (vmPFC) and impaired myelination in the ACC of depressed suicides (DS). Given that mature PV networks are stabilized by axonal myelination and PNNs, we hypothesize that CA has a lasting impact on PNN-myelin relations in the vmPFC. Well-characterized vmPFC samples from adult DS-CA, DS, and healthy controls were obtained from the Douglas-Bell Canada Brain Bank. Immunofluorescent (IF) labeling (PV, MBP, WFL, Neurofascin), multiarea timelapse z-stack images, and the Simple Neurite Tracing plugin (Fiji) are being used to investigate the relationship between PV axon myelination and PNN coverage. Our results show that in healthy control samples, most (81%) PV interneurons are myelinated and, of these cells, 63% are covered by a PNN. We are currently investigating this relationship in DS-CA and DS samples. These preliminary results suggest a potential relationship between PNNs and PV interneuron myelination. Further research in DS and DS-CA samples will provide greater insight into possible maladaptive changes in the PNN-myelin relationship.

P1-C-92: Cannflavin treatment normalizes alterations in neuronal systems function in vitro and behaviour in the valproic acid model of autism spectrum disorder

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Autism Spectrum Disorders (ASD) show significant variability in presentation, with existing therapies being inefficacious in treating the core symptoms. There is interest in cannabis compounds as novel therapies in ASD with a major focus being on cannabidiol. We evaluated the effects of the low abundance flavonoids, cannflavin A (CannA) or cannflavin B (CannB), on dendritic morphology and neuronal activity in vitro using the valproic acid (VPA) model of ASD. Cortical cultures were generated from sexed VPA-exposed rat pups and were untreated, or treated acutely (100nM) or sub-chronically (1nM) with CannA, CannB, or vehicle. Untreated VPA neurons had lower dendritic branching and greater neuronal activity with enhanced effect in the female VPA cultures. Sub-chronic CannA and CannB treatment increased dendritic branching in male, but not female, VPA-derived cortical cultures. Acute or sub-chronic CannA or CannB treatment normalized elevations in neuronal activity in VPA cultures with sex-dependent effects. Preliminary in vivo findings from adolescent male and female VPA rats exposed to acute CannB administration (0.2 mg/kg i.p.) showed improved sociality. These findings demonstrate that the cannflavins can normalize VPA-induced alterations in cortical neuronal architecture and activity and

may improve sociality in adolescent VPA rats. Future expanded in vivo behavioural and systems function studies will evaluate the potential of the cannflavins as a novel therapeutic in ASD.

P1-C-93: Neuregulin-1 Ameliorates Cognitive Decline In Chronic Cuprizone Mice by Augmenting Hippocampal Neurogenesis

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Progressive multiple sclerosis (PMS) is associated with neurodegeneration, brain atrophy and cognitive decline such as memory impairments. Neural precursor cells (NPCs) support continuous adult neurogenesis, and decline in their number and/or activity is an underlying cause for PMS associated cognitive deficits. We previously showed that Neuregulin-1 (Nrg-1) is dysregulated in MS brain lesions. Nrg-1 is important for neural differentiation, and its dysregulation has been associated with neurodevelopmental psychiatric disorders. Here, using cuprizone (CPZ) mouse model of PMS and primary culture of NPCs, we aimed to determine: 1) whether prolonged demyelination impacts neurogenesis, and 2) whether Nrg1 treatment can promote NPC activities and restore cognition decline. We induced CPZ demyelination in tamoxifen inducible Nestin-Cre transgenic mouse to track NPCs. We delivered Nrg-1 subcutaneously to mice that received 10 weeks of CPZ diet. Our cellular, molecular and neurobehavioural analyses in chronic CPZ mice showed significant brain atrophy and neurodegeneration with a concomitant decline in spatial and recognition memory. In vitro neurosphere assay on hippocampal NPCs isolated from CPZ mice showed smaller number of NPCs and reduced neurogenic capacity. 4 weeks of daily Nrg-1 treatment resulted in a significant increase in proliferation and neurogenesis of hippocampal NPCs in vivo and in vitro, which was also associated with attenuation of neurodegeneration and hippocampal atrophy. Importantly, Nrg-1 treatment restored cognitive impairments in CPZ mice to the same level as healthy mice. These findings identify the potential of Nrg-1 treatment in enhancing neurogenesis in progressive demyelinating conditions and its promise as a novel therapeutic strategy to ameliorate

P1-C-94: Interaction between alternative splicing and gene networks in major depressive disorder

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Previous work showed that the transcriptional organization of gene networks is affected differently in males and females with MDD, and that alternative splicing (AS) produces distinct mRNA molecules that encode proteins with different functional properties. This suggests that AS variants could contribute to the gene network organization across several tissues, including brain regions in both sexes. Here, we quantified the exon expression and characterized the AS events in males and females with MDD. A genome-wide gene expression dataset from 6 brain regions, including more than 600 human post-mortem samples from males and females with and without MDD, was analysed using Limma (exon) and rMATS (event). Our analysis showed that the representation of exons differs significantly between males

and females. We also identified striking differences between AS events, in which females with MDD showed an increase of total events when compared to males with MDD. In the dorsolateral prefrontal cortex, increased exon skipping, alternative splice site and intron retention were found in females with MDD (i.e., SCN1A-AS1 and CTSL), while males with MDD showed a larger amount of mutually exclusive exons. Our analysis suggests that the representation of exons and splicing events differs significantly between males and females across all studied brain regions. Understanding this could elucidate the molecular mechanisms that contribute to the expression of MDD, and ultimately improve treatment efficacy.

P1-C-95: Novel antioxidant co-drug VANL-100 elicits cytoprotective effects against beta-amyloid-induced toxicity

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Antioxidants are being explored as novel therapeutics for neurodegenerative disorders such as Alzheimer's disease. Recently, strategies such as chemically linking antioxidants to synthesize novel co-drugs have been tested. The objective of this study was to investigate the cytoprotective effects of VANL-100, a novel co-drug produced by covalently linking naringenin (NAR) and alpha-lipoic acid (ALA), in a cellular model of beta-amyloid (Aß)-induced toxicity. The effects of VANL-100 were compared to its parent compounds NAR and ALA, and activation of the Nrf2 pathway, a primary regulator of the endogenous antioxidant defence system, was explored as a potential mechanism of protection. Cytotoxicity was measured using the 3-(4,5-dimethylthiazol-2-yl)2-5-diphenyl-2H-tetrazolium bromide (MTT) assay. SH-SY5Y cells were either pre-treated with NAR, ALA or NAR+ALA for 24 hours prior to the addition of 20 micromolar Aß25-35 or co-treated with the antioxidant compounds and Aß25-35. Pre-treatment and co-treatment with VANL-100 significantly attenuated Aß-induced cell death, with no significant differences between the protective effects of VANL-100, NAR, ALA and NAR+ALA or between pre-treatment and co-treatment. Expression levels of total and phospho-Nrf2, KEAP1 and downstream targets such as heme oxygenase-1 were measured by western blot analysis. Early findings suggest VANL-100 may elicit protection via activation of the Nrf2 signalling pathway. These results demonstrate the novel co-drug VANL-100 protects against Aß-induced toxicity.

P1-C-97: Microglia indirectly maintain the increased recruitment of perineuronal nets associated with early life stress in both human and mouse prefrontal cortex

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Background: We recently reported that child abuse (CA) is associated with an increased recruitment of perineuronal nets (PNNs) in the ventromedial prefrontal cortex (vmPFC) of depressed suicides. Lately, microglia (MG) have been implicated in the maintenance and degradation of PNNs. We explored whether CA might affect MG-PNN interactions through spatial proximity and pruning or by release of

matrix metalloproteinases (MMPs). Methods: Well-characterized adult male (M) and female (F) vmPFC samples from depressed suicides with (DS-CA) or without (DS) a history of CA and matched neurotypical controls were obtained from the Douglas-Bell Canada Brain Bank. M and F C57BL/6 mice underwent limited bedding and nesting from postnatal day (PD) 2-9 and were sacrificed at PD 70. Immunofluorescence, ELISA, MMP antibody array, immunoblotting and fluorescent in-situ hybridization were used to examine MG-PNN interactions. Results: Human MG activation status (CD68+), density and spatial analysis did not differ by group, suggesting an indirect MG-PNN relationship. MMP-9 expression was downregulated in both DS-CA vmPFC grey matter samples and MG (CD11b+ pulldown). Western blot revealed a significant decrease in the neo-epitope of aggrecan cleaved by MMPs in DS-CA samples. ELS mice showed significant increase in PNNs in the mPFC while MG density and spatial analysis were unchanged. Conclusion: These results strongly suggest that MG play an indirect role in the maintenance of vmPFC PNNs in people with a history of CA, and data derived from an ELS mouse model support this conclusion.

P1-C-98: Non-biased investigation of cortico-accumbal and cortico-tegmental inputs in response to stress

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Chronic variable stress (CVS) induces morphological and functional changes in the cortico-accumbal and cortico-tegmental pathways. We investigated the upstream neural circuitry of both pathways to understand which inputs are affected by stress and may contribute to these effects. We used a 21-day CVS model to stress female mice. Inputs targeting neurons from the medial prefrontal cortex (mPFC) projecting to the nucleus accumbens (NAc) or ventral tegmental area (VTA) were identified through a combination of a trans-sectional viral approach and rabies trans-synaptic tracing. c-Fos immunohistochemistry was combined with whole brain light sheet microscopy to map the neuronal inputs projecting to NAc- or VTA-projecting cells. Cortico-tegmental cells are targeted by inputs from the insular cortex (INS), whereas the orbital area (ORB) projects more densely to NAc-projecting neurons. Limbic areas such as the entorhinal area and amygdala (AMY) also project densely to both pathways. C-Fos expression was lower in neurons from the INS and higher in neurons from the AMY projecting to cortico-tegmental neurons. In contrast, higher c-Fos expression was found in neurons from the ORB projecting on cortico-accumbal neurons. Overall, we mapped the neuronal circuits projecting on cortico-accumbal and tegmental pathways. Our analyses revealed how stress impacts the activity of these circuits, which may contribute to the morphological and functional changes affecting mPFC neurons projecting either to NAc or VTA and ultimately to the elaboration of stress responses.

P1-C-99: Spatial and topological analysis of astroglial scars following brain injury

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Quantitative analysis of glial reactivity and subsequent scar formation is of fundamental importance for understanding the dynamics of central nervous system (CNS) repair after injury. Herein, we developed a novel approach based on point pattern analysis (PPA) and topological data analysis (TDA) to quantify the spatiotemporal patterning of scar-forming cells. We validated our approach in ischemic stroke induced by the middle cerebral artery occlusion (MCAO) in C57BL/6J mice. We stained neurons (NeuN), microglia (IBA1), and astrocytes (GFAP) in fixed-frozen brain sections and performed alienation to the Allen Mouse Brain Atlas. We computed geometrical and topological features from cell positions at different time points after MCAo using 3-D PPA methods and persistent homology. Specifically, we used K-functions and Gaussian-smoothed Betti curves (which track connectivity and the presence of voids in data) to obtain a multiscale, interpretable summary of the spatial distribution of each cell type. Our preliminary results reveal that astrocytes and microglia exhibit different spatial responses following injury. We observed an inverse spatial correlation between GFAP+/NeuN+ and IBA1+/NeuN+ regions, suggesting that reactive astrocytes and microglia establish two distinct compartments. Furthermore, the time-dependent spatial correlation between GFAP+ and IBA1+ cells is consistent with reactive astrocytes progressively constraining reactive microglia to the injury core. Both glial cells mutually exhibit exclusive clustering below 600 µm but remain independently distributed above 900 µm, indicative of a transition from short- to long-range cell organization. Finally, we demonstrate that latent representations obtained from geometric and topological features of cell positioning

P1-C-100: Fatty acid composition in phospholipid fractions of white matter tracts in the human brain: a study of age and early life adversity

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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 findings may represent alterations of the myelin lipid profile, given that the composition of fatty acids (FA) in myelin phospholipids (PL) influence its compactness, stability, and permeability. Therefore, the objective of this study is to quantify FA concentrations in the postmortem human uncinate fasciculus (UF), a major association white matter tract, and characterize the relationships with CA and age. FA concentrations in all major PL pools 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 and separated into respective PL fractions using thin-layer chromatography. Fatty acid methyl esters from each fraction were quantified using gas chromatography-flame ionization detection. PL fractions revealed divergent patterns of FA composition with respect to CA, which diverged from those of cortical white matter. The FA composition of each PL fraction varied with age in different patterns, albeit with some overlap in FAs including arachidonic acid, adrenic acid, other polyunsaturates. We present the first ever characterization of UF FA

in each PL fraction and describe their relationships with CA and age. This data will be supplemented with cholesterol quantification as well as myelin ultrastructure to better understand their biological relevance.

P1-C-101: Somatostatin receptor 4 induces neuritogenesis and regulates the translocation of synaptophysin in amyloid-beta-treated SH-SY5Y cells

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive loss of neuronal processes and perturbed neurogenesis accounting for impaired cognitive function and memory loss. We recently described the role of somatostatin (SST) in promoting neurite outgrowth and expression of microtubule-associated proteins (MAPs), however, the mechanism remains elusive. We propose that SST via activation of SST receptor 4 (SSTR4), which is highly expressed in the brain and decreases in the AD brain might play a determinant role in preserving neurites. Briefly, SH-SY5Y neuroblastoma cells were treated with SSTR4 agonist during the 5 days of differentiation with and without amyloid-beta (Aβ) and processed for the expression and localization of synaptophysin (SYP) and MAPs expression. We observed that SYP in the presence of Aβ, is trapped in the trans-Golgi network (TGN) and failed to translocate to neurites. Our results showed that SST and SSTR4 agonists preserved neurites formation, promoted SYP translocation from TGN to neurites, and regulated the expression of MAPs when compared to Aβ-treated cells. Comparable results were obtained with overexpression of SSTR4 whereas the SSTR4-mediated effect was significantly abolished with SSTR4 knockdown. Our work identifies SSTR4 as a key regulator of neurogenesis, SYP translocation, and maintaining neuronal integrity which could be a potential therapeutic target for restoring neuronal circuits and cognitive function in AD.

P1-C-102: Functional alterations of ependymal cells by antibodies from neuromyelitis optica patients

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Ependyma is the epithelial barrier separating cerebrospinal fluid (CSF) and brain parenchyma. It regulates key functions for the brain such as exchanges between CSF and parenchyma (water, metabolites, or toxic elements) and CSF circulation with synchronous ciliary beating. A role in inflammatory processes is also suspected. Neuromyelitis optica (NMO) is a severe neuroinflammatory condition associated with autoantibodies (NMO-IgG), mainly directed against aquaporin 4 (AQP4). NMO-IgG are known to trigger astrocyte dysfunction leading to demyelination and axonal loss. Interestingly, ependymal cells also express AQP4, and evidence of ependymal alterations have been reported in NMO patients. Thus, the aim of this study was to evaluate if antibodies from NMO patients alter ependymal functions. Two models of ependymal cells, i.e. rat primary cultures and adult rat ventricular wall explants were exposed during 24 hours to NMO-IgG purified from patient sera. Immunolabeling of key functional proteins, ependymal flow assay and RNA sequencing were used to evaluate ependymal alterations. Purified IgGs from healthy donors were used as controls. NMO-IgG exposure induced morphological

alterations and modified AQP4 and gap junction expression; altered cilia motility; activated pro-inflammatory cytokines and chemokines synthesis and induced functional alterations of gene sets related to cilia and metallic ions transport. Our results show that NMO-IgG directly induce alterations of ependymal functions and suggest an involvement of ependyma in NMO lesion formation.

P1-C-103: Relevance of an extracellular chaperone protein in different animal models of familial Amyotrophic Lateral Sclerosis.

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Amyotrophic lateral sclerosis (ALS) is a disease characterized by motor neurons degeneration. Peptidylprolyl cis/trans-isomerase A (PPIA) is a chaperone protein with intracellular isomerase activity. Previous works showed that PPIA is highly secreted in the CSF (cerebrospinal fluid) and expressed by motor neurons and glial cells in mutant SOD1 animal models of ALS. When secreted, PPIA binds to its receptor inducing motor neuron death. Although well characterized in SOD1 models, the relevance of this extracellular protein in other familial ALS models, is still unknown. Here we aim at characterizing the expression of PPIA and its receptor in animal models carrying familial ALS mutations in SOD1, TDP-43 and FUS genes. Mice were sacrificed at different disease stages. Lumbar spinal cord and CSF were analyzed by immunoblotting and immunofluorescence to investigate expression and localization of PPIA and its receptor. We observed that mice with mutant SOD1 and TDP-43 genes present high levels of PPIA receptor in the lumbar spinal cord. PPIA is expressed by neuronal and glial cells in mutant TDP-43 mice and released in the CSF. Interestingly, we did not observe an increased release of PPIA in the CSF of mutant FUS mice. Our results demonstrate that PPIA might be pathologically important in ALS forms implicating mutant SOD1 and TDP-43 genes, whereas its relevance might be lower in FUS-mediated cases. Moreover, given the localization of the receptor in motor neurons and astrocytes, we can hypothesize a higher susceptibility of these cells to the effects of extracellular PPIA.

P1-C-104: The cellular-molecular landscape of the living human brain in epilepsy

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Epilepsy is a life-altering disease, affecting up to 1 million people worldwide. Despite the introduction of new anti-epileptic drugs in recent decades, 30% of patients remain pharmacoresistant. One of the challenges in understanding and treating epilepsy is the differences in fundamental properties between mice and human neurons, as well as the difficulty to translate therapeutic approaches from rodent models to clinical trials. We therefore studied the underlying pathological mechanisms of epilepsy directly in living human brain tissue from patients undergoing surgery for pharmacoresistent epilepsy. In this study, we employed spatial transcriptomics and single nucleus RNA-seq techniques to analyze the molecular and functional properties of cell types in living human brain specimens. Through this analysis, we identified the molecular profile and spatial organization of rare interneuron populations, known to be

involved in epilepsy, in the human brain. Additionally, we used calcium activity imaging (GCaMP8m) to record seizure-like events at the single-cell level in human hippocampal brain slice cultures and manipulated interneuron activity using optogenetic stimulation (ChrimsonR). Our findings provide insight into the molecular and functional changes in cell types in the epileptic human brain, and will inform the development of novel therapeutic approaches for the treatment of pharmacoresistant epilepsy. Additionally, our study highlights the importance of studying fundamental pathological mechanisms directly in human brain tissue for a better understanding of this debilitating disease.

P1-C-105: Adeno-associated virus mediated gene expression in enteric neurons: Relevance to Parkinson?s Disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the aggregation of α-synuclein (α-syn) in multiple brain regions, including the substantia nigra which is linked to the classical motor deficits. However, some PD patients also develop gastrointestinal (GI) symptoms that precede the onset of motor symptoms, often by several years. This observation has prompted closer investigation of the early role of enteric α-syn in PD pathogenesis, and the possibility that GI pathology is carried from enteric neurons to the brain along the vagus nerve. In this study, we test whether systemic delivery of adeno-associated virus (AAV) vectors targeting α-syn expression can be expressed in the GI tract of mice to reduce enteric α-syn, thus providing a potential therapeutic strategy for PD. Mice expressing human wild-type α-syn or the A53T mutant (TgM83+/-) received a single intravenous injection of AAV9 vectors carrying α-syn-shRNA or an anti-α-syn nanobody sequence. AAV9-SNCA-shRNA-treated mice had reduced stomach α-syn but not in the small and large intestines when compared to mice that received a scrambled-shRNA control as shown through Western blot and immunofluorescence analyses. Expression of the AAV9-nanobody vectors is found mostly in nonneuronal cells in the small intestine but has greater neuronal expression than AAV1-eGFP-treated mice. These suggest that systemic anti-α-syn therapeutics can be expressed in enteric neurons by AAV vectors to reduce α-syn. Future experiments may test whether enteric α-syn knockdown has a prophylactic effect when given prior to synucleinopathy triggered by fibril-seeding in the GI tract. Systemic α-syn knockdown can potentially be a useful minimally invasive gene therapy for PD.

P1-C-106: Calcium clearance deficits linked to endoplasmic reticulum stress are signature features of early retinal ganglion cell damage in glaucoma

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The mechanisms underlying retinal ganglion cell (RGC) vulnerability in glaucoma are poorly understood. We tested the hypothesis that RGC calcium (Ca2+) dynamics are affected in the early stages of ocular hypertension (OHT) and probed the mechanisms underlying this response. Two-photon laser scanning microscopy (TPLSM) was used to record light-evoked single-RGC Ca2+ dynamics in transgenic mice carrying GCaMP6f. OHT was induced by intracameral injection of magnetic microbeads, and Ca2+ signals were recorded two weeks later, before RGC loss. TPLSM imaging was performed in living anesthetized mice and ex vivo in retinal explants. Ca2+ parameters such as decay time (Ca2+ clearance) were computed. A set of approaches was used to examine RGC-specific pathways, including single-cell-RNAseq. Live trans-scleral and ex vivo imaging showed consistent defects in Ca2+ clearance across all RGC types. Analysis of molecular pathways revealed an RGC-specific reduction in gene and protein expression of the endoplasmic reticulum (ER) Ca2+ ATPase 2 (SERCA2), which is responsible for pumping Ca2+ from the cytoplasm to the ER. Loss of SERCA2 was accompanied by upregulation of the ER stress markers including CHOP. TPLSM recordings in naïve mice treated with a pharmacological inhibitor of SERCA2 showed Ca2+ clearance impairment in RGCs, recapitulating the effect of OHT. In contrast, glaucomatous eyes treated with a SERCA2-specific activator restored the ability of RGCs to reduce cytoplasmic Ca2+ to physiological levels effectively. Our study reveals defective Ca2+ clearance as a signature feature of early RGC damage, a trait conserved across RGC subtypes, and suggests that loss of SERCA2 has a profoundly detrimental effect on the ability of these neurons to regulate cytoplasmic Ca2+.

P1-C-107: Chronic variable stress induce sex-specific morphological and functional modifications in sst and pv interneurons in the mPFC

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There is increasing evidence that points toward alterations in the excitatory/inhibitory (E/I) balance, e.g., hypoactivity or hyperactivity of the mPFC, as a consequence of chronic stress. Still, little is known on the sex-specific impact of chronic stress on morphological and functional properties of the gatekeepers of E/I balance, the SST and PV interneurons, and their role on the regulation of emotional responses. We used 21 days of the chronic variable stress model (CVS) to induce an emotional stress response in PV-cre and SST-flpo transgenic mice. Compared to control animals, our analyses revealed a reduction in the complexity and dendritic arborization of SST interneurons in both male and female stressed mice. Conversely, we observed an increase in the number, complexity and dendritic arborization of PV interneurons in stressed female mice compared to controls, while stressed males exhibited reduced complexity and dendritic arborization when also compared to controls. Finally, we used mammalian GFP reconstitution across synaptic partners (mGRASP) and Stimulated emission depletion microscopy (STED) microscopy to assess neuronal complexity and functional alterations in stressed male and female mice. Our results show an increased number of excitatory synapses in pyramidal neurons from both sexes of stressed mice when compared to controls. Our results provide a better understanding on how chronic stress affects morphological and functional properties of SST and PV interneurons and their relationship with excitatory pyramidal neurons in a sex-specific way to modulate emotional responses.

P1-C-108: Altered network function and electrophysiological properties of corticomotor neurons in C9orf72 loss-of-function and gain-of-function ALS mouse models

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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 C9orf72 knockout loss-of-function (C9-KO LOF) and gain-of-function (C9-GOF) mouse models, 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 lower in the C9-GOF mice compared to wildtype mice, highlighting cortical hypoexcitability at this timepoint. Moreover, we have found a significant reduction in miniature inhibitory postsynaptic current frequency in the C9-GOF mice compared to wildtype mice, indicating impaired basal inhibitory network function. Finally, 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 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.

P1-C-109: Altered cortical excitation in the zQ175 Huntington Disease mouse model

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Huntington Disease (HD), manifests as motor dysfunction, cognitive impairment, and neuropsychiatric symptoms. The earliest synaptic and circuit changes which proceed symptomology occur in the striatum and cortex. Previous studies have indicated progressive changes in spontaneous excitability input in the cortex of N-terminal transgenic HD models (R6/1 and R6/2); however, much is unknown about these cortical changes in knock-in strains. Here we performed slice recordings from layer 2/3 cortical pyramidal neurons (CPN) from the sensory cortex of both male and female zQ175 (HD) and wildtype (WT) littermates aged 7-9 months. We found evidence of reduced cortical excitability in HD compared with WT mice. Intrinsic excitability in CPN was decreased, with higher rheobase and reduced number of action potentials fired in response to depolarizing current steps. Recordings from these CPNs also showed reduced spontaneous excitatory input. Previously in Sepers et al. 2022, we further showed no difference in spontaneous inhibitory input, overall suggesting a decreased excitation-inhibition (E-I) ratio. Pharmacology and/or whole-cell current voltage (IV) relationships using hyperpolarizing voltage steps

suggest changes in GABA-A and K channels (Kirs and HCN) should be examined and may in part explain changes in E-I ratio seen in HD mice. At this age, HD mice have been reported to have aberrant cortical activity response to sensory stimulation compared to WT and are generally accepted to be in the motor manifest stage. It would be interesting to determine the contribution of these excitability changes in slice to cortical activity changes imaged in vivo. Canadian Institutes of Health Research PJT-178043 to LAR; Hereditary Disease Foundation Fellowship award to JPM; Vanier award to YW

P1-C-110: Distinct and shared cell type specific transcriptomic changes in the postmortem dorsolateral prefrontal cortex of males and females with major depressive disorder

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Major depressive disorder (MDD) affects almost 300 million people worldwide, is a leading cause of disability globally, and increases suicide risk. Women are more at risk for MDD while men are more at risk for suicide. In human postmortem studies and in rodent MDD models, MDD-associated gene expression changes in multiple brain regions have shown sex-specificity. Imbalance in neuronal excitation and inhibition, astrocytic impairments, white matter disruption, neuroinflammation, and altered blood brain barrier integrity have been reported in MDD, implicating the majority of highly functionally specialized cell types in the human cortex. To elucidate cell type and sex specific MDD-associated gene expression changes we performed single-nucleus RNA-sequencing (snRNA-seq) in female subjects (20 MDD, 18 neurotypical) and combined these data with a previously published cohort of males (17 MDD, 16 neurotypical). The new and expanded dataset encompasses over 160,000 cells across 41 cell type clusters. Differential expression analysis implicated microglia and parvalbumin interneurons in females and confirmed the implication of deep layer excitatory neurons and oligodendrocyte precursor cells in males with MDD. Metanalysis revealed similarities in overall patterns of cell type specific MDD-associated changes across both sexes despite the prominence of distinct cell types in each sex individually. Novel results in females were supported by complementary weighted gene co-expression network analysis and pointed to the involvement of immune function and cellular stress related pathways.

P1-C-111: Unlocking the regenerative potential of the mammalian retina

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Currently, there are no treatments available to cure retinal degenerative diseases. In fish and frogs, adult Müller glia mediate natural retinal regeneration by responding to retinal insult and replacing any lost cell types, essentially acting as bona fide adult retinal stem cells. Unfortunately, mammalian Müller have lost this ability to self-heal and remain quiescent following retinal injury. Our goal is to understand why

mammalian Müller glia have lost this regenerative ability and subsequently activate them to regenerate lost neurons. Here, we report that the late-stage temporal identity factor Casz1, which functions to control cell fate choice during development, is upregulated following injury in mammalian Muller glia but not in fish. Additionally, we have confirmed that this expression is not limited to one type of injury but present even in the genetic ablation of photoreceptors such as in Rd1 mice. Being a transcription factor, Casz1 is found in the nucleus, and given its previous role in chromatin remodelling during development, we show that Casz1 expressing Müller glia have fewer chromocenters, but an overall increase in total heterochromatin area. Furthermore, Müller glia specific knock-out (KO) of Casz1 results in trans-differentiation of Müller glia into neuronal cells. These data suggest that Muller glia specific expression of Casz1 results in chromatin remodelling events that abrogate the accessibility of regenerative factors, and thus aborts the regenerative response to recover. lost neurons Overcoming this inhibitory response might help restore regenerative potential in mammalian Müller glia, which could be used as a novel therapy for retinal degenerative diseases.

P1-C-112: Endocannabinoid system and blood-brain barrier in chronic stress and depression

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Major depressive disorder (MDD) affects 300 million of people and is now considered the main cause of disability worldwide with only 30% of treated individuals completely recovering. Chronic stress, the main environmental risk for MDD development, has been known to trigger neurovascular pathology promoting development of depressive-like phenotype in mice. Those pathological changes have been confirmed in brain samples of MDD patients. However, biological mechanisms underlying these molecular changes in response to stress remain elusive. Thus, we decided to study the endocannabinoid system (ECS), a crucial regulator of stress responses and neurovascular health. However, the role of neurovascular ECS in the context of stress and depression remains unknow. We set to elucidate if and how ECS may regulate stress response and depressive-like behaviour. First, we identified ECS target genes linked with chronic stress vulnerability vs adaptation utilizing transcriptomic screening validated with RNA scope and STED super resolution microscopy. Next, we performed viral-mediated manipulations in neurovasculature to confirm a causal role for ECS in development of depressive-like behaviours. Finally, we evaluated how current antidepressant treatments affect ECS targets and neurovasculature. Our results provide novel insight into the role of neurovascular ECS in development of depression pathology. 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.

P1-C-113: Role of neurosteroids in behavior and opioid use disorder

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Neurosteroids are endogenously expressed in the brain and divided into subclasses, including Androstanes and Pregnanes, based on their carbon backbone. They mediate their effects via interactions with key receptors in the nervous system including GABAA-receptor, NMDA-R and other important neuronal receptors such as σ1 receptor and TrkA. Ample evidence has shown that these steroids are implicated in regulating a wide range of behaviours, such as motivation and memory formation. Despite the growing evidence of their impact on brain function, most neurosteroids' activity and molecular target(s) remain largely unknown. North America is currently facing an opioid addiction crisis leading to more than 6,000 deaths in Canada annually. However, current treatments for opioid abuse are replacement therapies with limited therapeutical efficacy leading to a very high relapse rate of up to 91%. We have recently demonstrated a role for neurosteroids in opioid abuse. Treatment with an inhibitor of steroid production, finasteride, reduces consumption in both zebrafish and rats without affecting nociception. Our goal is to investigate the neurological function of these steroids in the regulation of cognitive behaviours and in neurological disorders such as opioid abuse. Using behavioural platforms, we investigate the impact of neurosteroid treatments on a range of behaviours, such as learning tasks as well as opioid self-administration. We are using a combination of pharmacological and genetic tools to dissect the molecular pathways driving their effect. Neurosteroids represent an exciting potential therapy for opioid dependence. Identifying the molecular targets and their endogenous functions are critical steps in developing a more targeted treatment for opioid abuse.

P1-C-114: Mechanistic convergence of depression and suicide risk on astrocyte fatty acid metabolism

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Genome-wide association studies (GWAS) show conceptual promise to identify novel mechanisms of depression, but have not yet achieved this potential. One explanation is that depression risk acts through complex expression networks, and GWAS-identified genes represent important components of these networks but in isolation are insufficient for their functional annotation. In this study we aimed to identify and characterize the networks through which GWAS-identified depression risk genes operate. We generated and characterized seeded co-expression networks of 349 depression risk genes across 11 brain regions. We used principal component regression analyses and Mendelian randomization to identify a causal relationship between the networks of two such genes (FADS1 and ZKSCAN8) and suicidal ideation. These networks were primarily expressed in astrocytes and enriched for functions related to fatty acid metabolism. Integrating these networks with single nucleus RNA sequencing data from depressed and control individuals identified astrocytic states strongly altered in depression. We then identified FGF signalling as a putative downstream effector of this astrocytic state on synaptic function. Finally through transcriptomic and genetic analyses we identify PPARA as a key regulator of this pathway and a therapeutic target in depression. In conclusion, we identify transcriptomic networks

associated with depression and suicidal ideation which affect synaptic function through fatty acid signalling in astrocytes and identify a therapeutic strategy to target this pathway.

P1-C-116: Altered imprinted gene Igf2 regulation by amyloid-beta 1-42 in Alzheimer's disease

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Reduced insulin-like growth factor 2 (IGF2) levels in Alzheimer's disease (AD) may be the mechanism relating age-related metabolic disorders to dementia. Since Igf2 is an imprinted gene, we examined age and sex differences in the relationship between amyloid-beta 1-42 (Aβ42) accumulation and epigenetic regulation of the Igf2/H19 gene cluster in cerebrum, liver, and plasma of young and old male and female 5xFAD mice, in frontal cortex of male and female AD and non-AD patients, and in HEK293 cell cultures. We show IGF2 levels, Igf2 expression, histone acetylation, and H19 ICR methylation are lower in females than males. However, elevated Aβ42 levels are associated with Aβ42 binding to Igf2 DMR2, increased DNA and histone methylation, and a reduction in Igf2 expression and IGF2 levels in 5xFAD mice and AD patients, independent of H19 ICR methylation. Cell culture results confirmed the binding of Aβ42 to Igf2 DMR2 increased DNA and histone methylation, and reduced Igf2 expression. These results indicate an age- and sex-related causal relationship among Aβ42 levels, epigenomic state, and Igf2 expression in AD and provide a potential mechanism for Igf2 regulation in normal and pathological conditions, suggesting IGF2 levels may be a useful diagnostic biomarker for Aβ42 targeted AD therapies. Keywords: Alzheimer's disease, mouse model, epigenetics, gene imprinting, insulin-like growth factor 2, DNA methylation, chromatin modification, amyloid beta, gene expression.

P1-C-117: Investigating immune cell-derived extracellular vesicles populations in the context of disability and central nervous system injury within relapsing-remitting multiple sclerosis patients

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Extracellular vesicles (EVs) are secreted from cells under both normal physiological and pathological conditions and have been investigated as disease biomarkers in various inflammatory diseases. Previous research in our lab has demonstrated that immune cell-derived EVs within blood plasma are increased in mildly disabled and untreated multiple sclerosis (MS), an immune-mediated disease of the central nervous system. The objective of the current study was to longitudinally measure immune cell-derived EVs over time in MS patients experiencing an increase in clinical disability or plasma neurofilament light chain (pNfL) levels, a marker of axonal injury. Using blood plasma and peripheral blood mononuclear cells (PBMCs) from relapsing-remitting MS patients (RRMS; n=17-19), EVs derived from various immune cell subsets and PBMC subsets were quantified via flow cytometry. Preliminary data revealed no significant changes within EV populations in RRMS patients that had an increase in disability over time (≥1-point change in EDSS score); in patients exhibiting an increase in pNfL a significant decrease was observed in CD4 T cell EVs. PMBC populations did not change over time nor did changes in PBMC populations correlate with changes in their respective EVs populations. Interestingly, the magnitude of

change in CD4 EVs was correlated with the magnitude of change in pNfL. To explore why increasing axonal injury was associated with a decrease in CD4 EVs over time, immune cell-derived EVs in cerebrospinal fluid of RRMS patients will be measured and certain trafficking receptors (e.g. CXCR3) will be investigated.

P1-C-118: Characterizing patterns of neural activity in midbrain organoids as a model for studying Parkinson's disease

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Human derived midbrain organoids (hMOs) are a promising tool that can be used to study Parkinson's disease (PD) on a patient specific level. Yet, much is unknown about how accurately hMOs recapitulate the human brain. In human models of PD, the progression of the disease leads to changes in neural activity. In this study, we aim to determine whether hMOs can capture these changes in neural activity associated with PD. We have generated hMOs using induced pluripotent stem cells derived from PD patients and their CRISPR corrected controls and recorded their network activity over the course of 9 months using a Micro-Electrode Array. Using custom Python scripts, we then compared these patterns of activity between mutant and control (CTL) hMOs. In organoids derived from patients carrying a synuclein triplication mutation, we see a decrease in overall activity across the organoid compared to their CTLs. However, mutant hMOs showed an increase in the strength of single neuron and population wide bursts, as measured by the number of bursts, the firing rate within a burst, and the duration of the burst. This suggests that although mutant hMO activity is decreased, the organization of neural activity is shifted towards strong bursting activity. These findings are complementary to neural activity described in mouse models of PD and may reflect compensatory mechanisms as a response to cell death. To test if this change in activity was due to a decrease in dopamine (DA) transmission, we treated hMOs with exogenous L-Dopa and recorded their activity before and after treatment. Here, we saw a decrease in both the number of bursts and population bursts in mutant hMOs but not CTLs, suggesting that the altered network activity in mutant hMOs may be due to decreased DA transmission.

P1-C-119: Mitochondrial dysfunctions in induced neurons derived from patients with idiopathic Parkinson's disease

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Parkinson's Disease (PD) is a neurodegenerative disorder for which the most important risk factor is aging. It is characterized by the loss of dopaminergic neurons in the substantia nigra as well as accumulation of α-synuclein. Approximately 90% of PD cases are idiopathic (iPD) and yet, most of what we know about PD pathophysiology stems from studies of monogenic cases. Using direct neuronal reprogramming to generate induced neurons (iNs) from patient fibroblasts, we have shown that PD iNs retain signs of cellular aging and exhibit autophagy impairment leading to pathological α-synuclein

accumulation. Here, we investigate dysfunctions in mitophagy which have been associated with familial forms of PD, although their contribution to iPD pathophysiology remains unclear. We assessed mitophagy alterations in iPD iN derived from n=17 iPD patients and n=10 controls using CCCP. Autophagic structures were quantified using high-throughput acquisition microscopy. Our results show that compared to control iNs, CCCP does not induce mitophagy in PD iNs, but induces an accumulation of mitochondria in LC3+ autophagic structures and a decrease in LAMP1+ lysosome-containing mitochondria in the iPD group. Altogether, this suggests alterations in mitophagy. Ongoing experiments are aiming at investigating the underlying mechanisms of these mitophagy impairments, as well as how this impacts other mitochondrial dysfunction in these cells. This study will shed light on the contribution of mitophagy and mitochondrial functions to the pathophysiology of iPD, and how this can be targeted for therapy.

P1-C-120: Multiple types of tissue-resident progenitors are mobilized during GDNF-induced regeneration of the enteric nervous system in the context of Hirschsprung disease

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Hirschsprung disease (HSCR) is a severe congenital malformation of the enteric nervous system (ENS) characterized by the absence of neural ganglia in the distal bowel. The lack of ENS ganglia is due to incomplete colonization by neural crest cells (NCCs) of vagal origin. NCCs of sacral origin and NCC-derived Schwann cell precursors (SCPs) can also contribute subsets of enteric neurons and glia, but neither of these additional sources can naturally compensate for the lack of vagal-derived ENS progenitors. Surgical removal of the diseased area is currently offered to patients, but this intervention causes permanent side effects such as fecal incontinence. We recently showed that rectal administration of GDNF (Glial cell line Derived Neurotrophic Factor) induces ENS ganglia containing neurons and glia in the otherwise aganglionic bowel of three HSCR mouse models. Cre/LoxP-based cell lineage tracing revealed that DHH+ SCPs could be a source of GDNF-induced ENS in this context. Using single-cell RNAseq combined to genetic cell lineage tracing, we now show that GFAP+ cells scattered in the aganglionic region can also be targeted by GDNF. These GFAP+ progenitors can generate ~⅓ of all induced neurons, like SCPs. Other data suggest that some of these GFAP+ progenitors are in fact derived from SCPs. Moreover, we found that neither SCPs nor GFAP+ cells are the first to differentiate into neurons, suggesting another source of GDNF-targeted progenitors. All these findings provide an important advance in the search for a regenerative therapy that could replace surgery for HSCR.

P1-C-121: Early changes in firing properties of VIP interneurons and abnormal CA1 inhibition in asymptomatic 3xTg-AD mice

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The 3xTg-AD mouse model is used to study Alzheimer's disease (AD), as at advanced stage, mice display some cognitive deficits and neuropathological hallmarks similar to those seen in human AD patients. AD is characterized by a progressive memory loss, with hippocampal hyperactivity being considered as one of the earliest pathophysiological processes in both human and animal studies. Various types of GABAergic interneurons are involved in coordination of network activity in the hippocampus. The type 3 interneuron-specific (IS-3) cells co-express vasoactive intestinal peptide and calretinin, and play an important role in memory formation as, by providing disinhibition to principal excitatory cells, they can gate the inputs arriving to the hippocampal CA1 region. Whether the activity of these cells is altered in AD remains unknown. Here, we addressed this question by examining the properties of IS-3 cells, their target - oriens/alveus (O/A) interneurons - and excitatory pyramidal (PYR) neurons in young asymptomatic 3xTg-AD mice. Our data indicate that whereas the density and morphological characteristics of IS-3 cells in 3xTg-AD mice remain unaltered, the IS-3 firing output can show significant changes. The latter was associated with a decreased inhibitory drive to O/A interneurons. Furthermore, using wireless fiber photometry calcium imaging in freely behaving mice, we observed changes in the activity of CA1 O/A interneurons and PYR neurons in 3xTg-AD mice during different behavioral states. Together, these data indicate that the altered IS-3 cells' firing output in 3xTg-AD mice may be responsible for abnormal activity of hippocampal CA1 interneurons and PYR neurons and can potentially lead to excitation/inhibition imbalance and further mnemonic dysfunction.

P1-C-122: Molecular, cellular and behavioral characterization of autism-related anomalies in two mouse models of CHARGE syndrome

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CHARGE syndrome (CS) is a rare genetic disorder characterized by a complex set of clinical features. One poorly understood hallmark is intellectual disability related to autism spectrum disorder (ASD). The Fam172aTp/Tp and Chd7Gt/+ mice recapitulate the human pathology, including behavioral issues (e.g., hyperactivity and aggression) and structural brain defects (e.g., cerebellum hypoplasia). The goal of this study was to identify and characterize shared behavioral and structural cerebellum anomalies in both CS mouse models. Various behavioral tests were used to evaluate locomotor activity (open field maze), anxiety (elevated plus maze), repetitive behavior (marble burying) and social deficits (three-chamber social interaction). H&E staining and immunostaining with specific neural markers were used to define structural and cellular defects in the cerebellar vermis of the mutants. Our findings revealed that both mutants are hyperactive and less anxious. This hyperactivity notably involves excessive spinning, which was found to be a confounding factor in the repetitive behavior test. Both mutants also exhibited a significant reduction in sociability and in preference for social novelty. Furthermore, both mutants display a common malformation in the lobule IX of the cerebellar vermis. This malformation is accompanied by the mis-localization of the three main cell types in the cerebellum (glial Bergman cells, and neuronal Purkinje cells and granule cells). Our finding thus points to cerebellar vermis anomalies as a cause of behavioral impairments associated with ASD in CS.

P1-C-123: Neural stem cell-mediated oligodendrogenesis for adult brain remyelination: the role of the niche environment

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Adult neural stem cells (NSCs) in the mammalian ventricular-subventricular zone (V-SVZ) produce myelinating oligodendrocytes. Understanding how NSCs generate oligodendrocytes represents a potential therapeutic avenue for neurological conditions involving myelin damage and oligodendrocyte loss. Using lineage tracing and single-cell transcriptomic profiling, we examined the oligodendrogenic potential of V-SVZ NSCs at homeostasis and following cuprizone-rapamycin induced demyelination. We assessed the V-SVZ environment via ligand-receptor communication analyses and screened predicted ligands using in vitro cortical precursor proliferation and oligodendrogenesis assays. We show that following demyelination, NSCs are activated and make 3-fold more oligodendrocytes than they do at homeostasis. The transcriptional profiles of NSCs and their neural precursor progeny are unaltered following demyelination. However, there are major alterations in V-SVZ-expressed ligands. The largest changes involve microglia; microglia numbers increase about 3-fold, and qualitatively change the ligands they express. Our in vitro data shows a 50% increase in proliferating cells and 66% increase in oligodendrocyte precursor cells after treatment with predicted microglial ligand, Oncostatin M (OSM). These data indicate that NSCs do not fundamentally change their cell identity following demyelination and suggest the importance of the niche environment in determining NSC fate and remyelination. We are currently validating the effect of OSM by infusion into the V-SVZ in normal and demyelinating conditions.

P1-C-124: Investigating the function of polymorphisms in APOE in chronic pain

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Activation of microglia in the spinal cord following peripheral nerve injury is critical for the development of long-lasting pain hypersensitivity. Single cell RNA sequencing of isolated microglia revealed that Apolipoprotein E (Apoe) is the top upregulated gene in spinal cord microglia at chronic time points after peripheral nerve injury in mice. APOE is a lipoprotein that is essential for the regulation of neuroimmune functions, synaptic activity, and aging. In humans, there are 3 different isoforms of APOE: APOE-ε2, APOE-ε3 and APOE-ε4. Previously we have shown that carriers with APOE-ε2 have significantly higher risk to develop chronic pain, whereas carriers of APOE-ε4 have lower risk to develop distinct chronic pain conditions. This is opposite to what is found in Alzheimer's disease with APOE-ε4 being the strongest genetic risk factor. To test the functional role of ApoE polymorphisms in chronic pain, we used humanized mice expressing APOE-ε2, APOE-ε3 and APOE-ε4, and implemented four models of chronic pain: spared nerve injury (SNI), Complete Freund's Adjuvant (CFA), hyperalgesic priming, and chronic constriction injury (CCI). Behavioral testing conducted at baseline revealed an increase in cold sensitivity in APOE-ε2 mice. Following behavioral testing in mice with SNI, APOE-ε4 mice showed a decrease in

nerve-injury induced cold hypersensitivity. Furthermore, hyperalgesic priming in APOE-ε4 mice showed reduced mechanical allodynia. Our results support epidemiological studies in humans as they show that carriers of APOE-ε2 promotes hypersensitivity whereas carriers of APOE-ε4 is protective against developing chronic pain. Altogether, these studies might facilitate better diagnosis and treatment of individuals living with different chronic pain conditions.

P1-C-125: Repeated mild traumatic brain injuries during adolescence could contribute to the development of MS-like pathology later in life

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Retrospective patient studies have identified single or repeated mild traumatic brain injuries (RmTBIs), especially during childhood and adolescence, as risk factors for MS. In addition, there is accumulating evidence that RmTBIs can drive chronic neuroinflammation, myelin- and axonopathy, and increase the risk of developing neurodegenerative diseases later in life. The overarching hypothesis of this project proposes that RmTBIs during adolescence can drive the development of autoreactive immune responses against CNS-derived antigens, resulting in MS-like pathology. I aim to test this hypothesis using the lateral impact model of RmTBIs in adolescent mice, first assessing via immunohistochemistry microglia and infiltrating immune cell responses at various timepoints following injuries, as well as the extent of diffuse axonal injury and myelin disruption. In addition, I aim to investigate how adolescent RmTBIs given prior to the induction of EAE (using MOG/CFA and PTX) will influence the onset and progression of, EAE pathology. Overall, I anticipate this research will extend the understanding of MS etiology, as well as inform research into the underlying neurodegeneration in MS, that will ultimately improve treatment strategies for progressive MS patients.

P1-C-126: Single-nucleus profiling identifies accelerated oligodendrocyte precursor cell senescence in a mouse model of Down Syndrome

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Down Syndrome (DS), the leading genetic cause of intellectual disability, is caused by triplication of human chromosome 21 (HSA21) and marked by chronic neuroinflammation, hypomyelination, and early-onset neurodegeneration. However, the precise mechanisms by which HSA21 triplication drives age-dependent cognitive decline in DS remain largely unknown. Using the Ts65Dn mouse model of DS, we performed an integrated single nucleus RNA- and ATAC-seq analysis of the 6-month cortex. We identified cell type-specific mRNA and chromatin-associated changes in the aged DS cortex, including regulators of transcription, translation, neurodevelopment, and inflammation. Changes in gene expression were evident, but not restricted to trisomic regions, suggesting complex global cascades that contribute to genome-wide regulatory and dosage compensatory mechanisms. We further discovered that cortical layer V-IV oligodendrocyte precursor cells (OPCs) exhibited accelerated senescence, reduced proliferation and heterochromatin, loss of nuclear LaminB1, and enrichment of a senescence-associated

transcriptional signature. Using highly multiplexed in situ imaging, we further defined the spatial architecture of the DS brain, identifying immunomodulatory gene signatures in cortical OPCs. Treatment of Ts65Dn mice with fisetin, a senescence-reducing flavonoid, rescued cortical OPC senescence activity. Together, these findings define previously uncharacterized cellular features of DS and suggest that cortical OPC senescence may be an important mediator of neuroinflammation and cognitive decline in DS.

P1-C-127: Expression of PPIA and its receptor is altered in the peripheral nervous system of SOD1G93A model of Amyotrophic Lateral Sclerosis

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Peptidyl-prolyl isomerase A (PPIA), a translational biomarker for amyotrophic lateral sclerosis (ALS), is a chaperone protein with cis/trans isomerase activity involved in protein folding and assembly. In the central nervous system (CNS) of ALS models (SOD1G93A mice) PPIA is highly expressed by motoneurons and glial cells. Once released, extracellular PPIA binds to its receptor, inducing proinflammatory events and the release of MMPs (matrix metalloproteinases). MMPs are known to be implicated in motor neuron death (MMP-9) and Schwann cells migration and myelination (MMP-7). The role of PPIA in the peripheral nervous system (PNS) during ALS is still unknown. This study assesses the expression of PPIA and its receptor in the PNS of SOD1G93A mice at different disease stages. Sciatic nerves and tibialis anterior muscles were collected from non-transgenic and SOD1G93A mice at different disease stages. Immunofluorescence (IF) staining and western blot (WB) experiments were performed to unravel the localization and the expression levels of the two proteins in PNS tissues. Both WB and IF analyses showed that the expression of PPIA and its receptor is altered in SOD1G93A PNS tissues with the progression of the disease. IF experiments revealed the presence of PPIA and its receptor in motor neurons and Schwann cells. Although preliminary, this study shows alterations of PPIA levels in the PNS of SOD1G93A mice. Given the relevance of PPIA (as an intra and extracellular protein) in the CNS of SOD1G93A mice, our results highlight a possible implication of PPIA also in the PNS.

P1-C-128: Molecular characterization of a novel gene causing mirror movements disorder

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During neurodevelopment, neurons extend axons in response to guidance cues to reach their target and make connections. The attractive axon guidance cue Netrin-1, acting through its receptor DCC, guides axons across the midline of the body. In humans, mutations in DCC and Netrin-1 account for about half of the cases of mirror movements (MM), a disorder characterized by the involuntary movement of a limb on one side of the body that mirrors the voluntary movement of the homologous limb on the opposite side. We hypothesized that the identification of new mutations causing MM might lead to the discovery

of novel genes functioning downstream of Netrin-1/DCC signaling. Through exome sequencing of MM patients, we identified a mutation in a gene encoding a guanine nucleotide exchange factor (GEF). GEFs promote the activity of Rho GTPases and help direct the cytoskeletal changes that orchestrate axon guidance. Consistent with our hypothesis, we showed that this GEF directly binds to DCC. In contrast, the MM-associated GEF variant loses its interaction with DCC. Using immunofluorescence imaging, we demonstrated that this GEF induces the relocalization of DCC from the plasma membrane to the cytoplasm, and that the MM GEF variant is significantly less efficient at inducing DCC relocalization. Furthermore, we showed that the GEF induces the activation of the Rho GTPase Cdc42, while the MM variant does not induce Cdc42 activation as efficiently. Thus, our results suggest that we have identified a novel downstream effector of Netrin-1/DCC signaling and that its mutation causes MM.

P1-C-129: Cannabinoids modulate cytotoxicity and neuritogenesis in amyloid-beta treated neuronal cells

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Introduction: The impact of neurodegenerative disorders, including Alzheimer's Disease (AD), on the Canadian economy is around $28 billion and is estimated to increase by ten folds in the next few years. AD is caused by toxicity and proteostatic collapse due to misfolded Amyloid beta (Aβ) protein. Studies have shown that Cannabinoids, via their cognate receptors (CB1R and CB2R), reduce Aβ toxicity, decrease p-tau, and inflammatory response, thus improving neuronal viability. Therefore, in the present study, we examined the role of cannabinoids on Aβ-induced toxicity using in vitro models. Methods: We used differentiated SHSY5Y and MC65 cells as in vitro models. MC65 cells contain a C-99 fragment of the APP under (tet)-sensitive promoter. Cells were treated with CBX for 24 hrs in a dose-dependent manner under Aβ-mediated cytotoxic insult and processed accordingly. Results: In the present study, we observed that CBX significantly increased cell survival under Aβ induced cytotoxic insults. Moreover, CBX treatment attenuates increased BAX expression in the presence of Aβ (5 µM), whereas it enhanced phospho-BCL2 levels alone or in the presence of Aβ. Moreover, CBX treatment improved neuritogenesis in control or Aβ treated cells, as evidenced by increased neurite length or enhanced expression of neurite markers, Tuj1 and MAP2. Summary: The results presented here demonstrate the anti-apoptotic effects of CBX and its role in neuritogenesis in the cells of neuronal origin and support the role of CBX as a potential therapeutic intervention in neurodegenerative diseases. COI: InMed Pharmaceuticals is commercializing cannabinoid-based therapies. RKS is a Research Consultant.

P1-C-130: Chemotherapy-induced postsynaptic-dependent impairment in synaptic function in the hippocampus

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Introduction: Chemotherapy-induced cognitive impairment, known as chemobrain, is a common side effect of cancer treatment. It is characterized by impaired memory, learning, and attention that can

persist for years after cessation of chemotherapy, adversely affecting a rapidly growing population of cancer patients and survivors. 5-fluorouracil (5FU) is a common component of first-line chemotherapy for many cancers and is known to induce chemobrain. We hypothesize that 5FU functionally impairs hippocampal synapses essential for cognitive functions. Methods: Mice were intraperitoneally injected with 60 mg/kg 5FU or saline (control). To determine acute effects, mice received one injection and assessed 1 or 7 days later. To determine chronic effects, mice received four weekly injections mimicking clinical chemotherapy regimen, and assessed 7 or 28 days after the last injection. Field EPSP was recorded ex-vivo at the hippocampal CA3-CA1 synapse to assess the effect of 5FU. Results: At 24h after a single dose of 5FU, basal fEPSP was inhibited with no change in paired pulse ratio or fiber volley, suggesting postsynaptic change. Long-term potentiation (LTP) was also significantly reduced. These 5FU effects reversed within 7 days. Repeated 5FU treatment induced similar synaptic impairment, however, the effects lasted at least 28 days. Synaptic structural analysis is currently underway to determine whether the observed functional deficits accompany structural changes. Conclusion: Our results suggest that 5FU induces cumulative impairment in hippocampal synaptic function in a postsynaptic dependent manner, which may underlie chemobrain. Understanding the cellular mechanisms underlying synaptic changes may lead to evidence-based therapeutic strategies against chemobrain.

P1-C-131: 17-beta estradiol activates AMPK and ATF3 and promotes neurite outgrowth of adult sensory neurons

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Dorsal root ganglion (DRG) sensory neurons express both estrogen receptors (ERs) alpha and beta in male and female rodents. 17-beta estradiol plays an important role in the development and survival of adult DRG neurons and regulates neurite outgrowth. AMP-activated protein kinase (AMPK) acts as a cellular energy sensor and can regulate the levels of activating transcription factor 3 (ATF3) and peroxisome proliferator-activated receptor γ coactivator-1 α (PGC-1α). These target proteins are involved in neuronal regeneration and mitochondrial biogenesis. We hypothesized that activation of ERs could increase the energy metabolism of DRG neurons and promote their axonal sprouting. DRG neurons from adult male or female Sprague Dawley rats were isolated and cultured under defined conditions. Immunocytochemical analysis confirmed the presence of both ERs alpha and beta. Treatment with 17-beta estradiol increased the levels of phosphorylated AMPK (pAMPK) in male or female DRG neurons in a dose dependent manner. Protein levels of ATF3 and PGC-1α were also elevated. Neurons derived from male or female rats exhibited elevated neurite outgrowth in response to estradiol treatment. This investigation reveals that 17-beta estradiol promotes neurite outgrowth via a pathway involving activation of pAMPK, PGC-1α and ATF3 in adult DRG neurons. These findings highlight potential therapeutic applications of 17-beta estradiol in alleviating neurodegenerative diseases, such as peripheral neuropathy. Funded by CIHR grant #PJT-162144.

P1-C-132: Transgenic expression of alpha-synuclein in retinal neurons

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Parkinson's disease (PD) is a common neurodegenerative disorder with progressive motor deficits linked to the progressive loss of nigral dopaminergic neurons and accumulation of aggregated alpha-synuclein (AS). Interestingly, visual deficits in colour vision, visual acuity, and contrast sensitivity are also reported and can precede motor dysfunction. An underlying retinal pathogenesis appears to play a key role in these symptoms. For example, PD patients have thinner ganglion cell (GCL), inner plexiform (IPL), and inner nuclear (INL) layers of the retina relative to healthy age-matched controls. To develop therapeutic targets for PD, this project seeks to (1) evaluate retinal AS expression in murine models with varying levels of human AS, (2) determine the mechanisms by which aberrant AS spreads between retinal neurons, and (3) assess whether the pathology can be visualized for use as a biomarker. I have performed immunostaining of murine retinas in combination with confocal microscopy to assess the expression of AS variants (human wild-type, human A53T-mutant, mouse) in different mouse strains, such as transgenic mice over-expressing human A53T mutant synuclein (TgM83), transgenic mice expressing human wild-type synuclein, wild-type mice, and synuclein-knockout mice. My initial results indicate that mouse synuclein is endogenously expressed in the IPL, but not the outer plexiform layer (OPL), while our transgenic mouse lines express human synuclein in both layers. Phosphorylated Ser129, an indicator of aggregated AS, is detected exclusively in the OPL of TgM83 mice. Next, we will undertake in vitro co-culture donor-acceptor experiments to understand how AS aggregates can spread from affected to healthy cells, then use neuronal transplants into retinas.

P1-C-133: A TrkB partial agonist rescues autistic-like behaviour in juvenile mice prenatally exposed to valproic acid

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by core symptoms including impaired social and repetitive behavior. Available ASD treatments do not treat the core symptoms. In humans and rodents, exposure to valproic acid (VPA) during pregnancy leads to idiopathic ASD in offspring. Brain-derived neurotrophic factor receptor (TrkB) and its signaling are decreased in idiopathic ASD. We hypothesized that the TrkB agonist, LM22A-4, would restore TrkB signaling and reduce autistic-like behavior in the VPA mouse model. Pregnant C57Bl/6 mice were injected intraperitoneally (i.p.) with VPA or saline (vehicle) on embryonic day 12.5. Offspring of both sexes received either daily i.p. injections of LM22A-4 or saline (vehicle). Behavioral assays included tests of anxiety (step-down test and elevated plus maze on postnatal days [PD] 29-30), repetitive behavior (marble-burying on PD31), sociability and locomotor activity (3-chamber test on PDs 32-33), and olfaction (buried food seeking test on PD34). Our results showed that VPA-exposed mice of both sexes exhibited impaired sociability and increased repetitive behavior. VPA mice did not show anxiety, locomotion, or olfactory deficits. Further, ASD-like core symptoms were prevented by LM22A-4

treatment. Our findings suggest that decreased TrkB signaling plays a role in the etiology of ASD.
Supported by a grant from the Pooler Charitable Foundation.

P1-C-134: The modulatory role of curcumin and quercetin on Drosophila GSK-3

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Key facets of Parkinson-associated neuroinflammation include oxidative stress and mitochondrial dysfunction, both known to be impacted by Glycogen synthase kinase 3 beta (GSK-3B) activity. Curcumin and quercetin, a common plant flavanol, have antioxidant activity. Drosophila with a loss of function mutations in GSK-3 have decreased locomotor and exploratory activities, oxidative damage, and a decrease in dopaminergic neurons, mimicking some features of Parkinson's Disease. We asked if treating these mutant flies improves locomotor and exploratory activities, provides antioxidant protection, and reduces the death of dopaminergic neurons. Methods: Drosophila were fed curcumin and quercetin and assayed for locomotor activity, the activities of reactive oxygen species, and we quantified the number of dopaminergic neurons in the adult brain using confocal microscopy. Results: The climbing index for mutant flies decreased significantly than those fed with standard diet and treated with both curcumin and quercetin. Moreover, curcumin and quercetin intervention increased the activities of anti-oxidative enzyme activity and inhibits lipid peroxidation. In addition, mutant flies fed curcumin and quercetin shows reduced inflammation and where more positive to dopaminergic neurons markers. and down-regulate the GSK-3, hence suggest the therapeutic potential of a synergistic treatment regimen. Discussion: Our data suggest that a combination of curcumin and quercetin or their derivatives may have therapeutic potential in the treatment of neurogenerative diseases.

P1-C-135: Non-psychoactive compounds of cannabis synergize with CBD enhance cognition and reduce the detrimental consequences of neuroinflammation

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Introduction: Cannabidiol (CBD) influences astrocytes' bioenergetic processes, providing some protection against neuroinflammation. One unresolved issue is whether it is possible to enhance CBD's protective effects against neuroinflammation that leads to cognition deficit, anxiety, and to astrocytic bioenergetics profile impairments. Given that CBD is only one of the many non-psychoactive compounds extracted from cannabis, we asked whether combining CBD with these compounds will provide better protection against the detrimental effects of neuroinflammation. Methods: GC/MS is used to identify a cannabis extract containing three non-psychoactive molecules together with CBD. 10 days before lipopolysaccharide (LPS) injection (i.p) to induce neuroinflammation, one group of mice was injected with cannabis extract and a second group with CBD, then tested for memory function and anxiety.

Astrocytes purified from mice were assayed for oxygen consumption and extracellular acidification rates. Results: Behavioral tests show that the extract exerts higher pro-cognitive effect compared to CBD but has a less anxiolytic effect. The extract exerts a more significant modulator effect on the astrocytic metabolic profile than CBD alone. It increased glycolysis, thus preventing the LPS-induced skew toward oxidative phosphorylation, and reduced LPS-induced mitochondrial ATP production. Conclusion: These findings suggest that the synergy of CBD with other non-psychoactive compounds enhances cognition and provides a more substantial attenuation of neuroinflammation by acting as a metabolomodulator.

P1-C-136: ADHD-related Lphn3 missense variants impair the receptor coupling to Gα13 and downstream actin remodeling

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Introduction: Specific mutations in the Latrophilin-3(Lphn3/ADGRL3) a member of the adhesion G Protein Coupled Receptor (GPCR) are associated with attention-deficit/hyperactivity disorder (ADHD). Lphn3 participates in the stabilization and maintenance of neuronal networks establishing interactions with transmembrane ligands. How these genetic alterations affect receptor function remains unclear. We hypothesize that downstream signaling of the Lphn3 receptor is defective in Lphn3 ADHD-associated variants. Methods: BRET and FRET based biosensors were used to determine the profile of coupling to G proteins and the RhoA activity shown by Lphn3 and variants, as well as confocal microscopy to evaluate actin-dependent structures. HEK293 cells were used as heterologous expression system. Results: We found that all ADHD-associated variants had normal coupling properties to Gαi, Gαs and Gαq. However, these variants showed coupling defects to Gα13 under both constitutive and ligand-dependent conditions. In addition, actin remodeling functions as well as RhoA signaling relevant for actin regulation normally displayed by the constitutively active Lphn3 receptor were impaired in the presence of specific variants. Discussion: Our results point to a selective signaling defect in the Gα13 pathway as a result of ADHD-associated variants suggesting that the interaction between the GPCR functions of Lphn3 and downstream remodeling of the actin cytoskeleton modulate neurodevelopmental cues as neural circuits are being established. Impairment in this interaction may lead to ADHD etiology.

P1-C-137: Correction of mTORC1-mediated brain protein synthesis rescues memory in mouse models of Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by synapse failure and cognitive decline. Brain mRNA translation is central to synaptic plasticity and cognition, and converging evidence

indicates it is impaired in AD. The mammalian target of rapamycin complex 1 (mTORC1) pathway plays a key role in regulating protein synthesis, and mTORC1 signaling has received considerable attention in AD research. In this work, we investigated whether stimulating mTORC1-mediated protein synthesis could alleviate the impairments in synaptic plasticity and memory in AD mice. To address this question, we used two different approaches: 1. genetic reduction of the translational repressors, Fragile X messenger ribonucleoprotein (FMRP) or eukaryotic initiation factor 4E (eIF4E)-binding protein 2 (4E-BP2); and 2. pharmacological treatment with (2R,6R)-hydroxynorketamine (HNK), an active metabolite of the antidepressant ketamine that stimulates mTORC1 signaling. Our results showed that genetic reduction of FMRP and 4E-BP2 prevented the inhibition of hippocampal protein synthesis and memory impairment induced by amyloid-β oligomers (AβOs) in mice. Reduction of 4E-BP2 further rescued memory deficits in the APPswe/PS1dE9 (APP/PS1) transgenic mouse model of AD. Moreover, HNK treatment prevented deficits in long-term potentiation (LTP) and fear memory in AβO-infused and APP/PS1 mice. Taken together, our findings indicate that strategies targeting mRNA translation correct hippocampal protein synthesis, synaptic plasticity and memory deficits in AD models, and raise the prospect that HNK could emerge as a therapeutic approach in AD.

P1-C-138: Severe COVID-19 patients with neurological symptoms display Alzheimers-like altered cerebrospinal fluid biomarkers

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COVID-19 induces acute and long-term neurological symptoms and may increase susceptibility to dementia and Alzheimer's disease (AD). Given that neuroinflammation, neurodegeneration, amyloid and Tau pathologies are AD molecular hallmarks, we asked if these biomarkers are altered in COVID-19. We investigated clinical and neuroimaging data from 35 hospitalized COVID-19 patients with neurological symptoms. We measured cerebrospinal fluid (CSF) biomarkers, including amyloid-beta (Aβ)1-42/1-40, pTau181, and Tau, and compared them to a pre-pandemic cohort (n=71) of non-demented controls, amnestic mild cognitive impairment (aMCI), or AD patients. COVID-19 induced heterogeneous neurological features associated with modified CSF hemostasis, innate immunity, and amyloidosis proteomic pathways. Patients showed higher CSF interleukin-6 (IL6) and tumour necrosis factor-alpha (TNF-α) than controls. CSF Tau was similarly elevated in severe COVID-19 and AD patients. Severe COVID-19, aMCI, and AD patients had decreased CSF Aβ1-42/1-40 ratios. Also, severe COVID-19 patients showed higher CSF IL6 and Tau, lower Aβ1-42 levels, and more pronounced neuroimaging alterations than mild patients. CSF IL6 and Tau correlated with CSF TNF-α, amyloid, and systemic inflammation. At one-year post-COVID, most survivors reported attention/memory deficits (n=13/19). Our study shows that CSF IL6, Tau, and amyloid connect COVID-19 neurological and systemic disease, offering molecular links between COVID-19 and AD-neurodegeneration. If unresolved, such alterations may favour AD development in COVID-19 survivors.

P1-C-139: Whole Exome Sequencing Reveals A Novel Homozygous Var-iant in the Ganglioside Biosynthetic Enzyme, ST3GAL5 Gene in a Saudi Family Causing Salt and Pepper Syndrome

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Salt and pepper developmental regression syndrome (SPDRS) is an autosomal recessive disorder characterized by epilepsy, profound intellectual disability, choreoathetosis, scoliosis, and dermal pigmentation along with dysmorphic facial features. GM3 synthase deficiency is due to any pathogenic mutation in ST3 Beta-Galactoside Alpha-2,3-Sialyltransferase 5 (ST3GAL5) gene, which is encodes sialyltransferase enzyme that synthesizes ganglioside GM3. In this study, Whole Exome Sequencing (WES) results presented a novel homozygous pathogenic variant NM_003896.3:c.221T>A (p.Val74Glu) in the exon 3 of ST3GAL5 gene causing SPDRS with epilepsy, short stature, speech delay, and developmental delay in all three affected members of the same Saudi family. The results of WES sequencing were further validated using Sanger sequencing analysis. For the first time, we are reporting the SPDRS in a Saudi family showing phenotypic features similar to other reported cases. This study further adds to the literature and explains the role of the ST3GAL5 gene which plays an important role, and any pathogenic variants may cause GM3 synthase deficiency that is leading to the disease. This study would finally enable the creation of a database of the disease that provides a base for understanding the important and critical genomic regions that will help control intellectual disability and epilepsy in Saudi patients.

P1-C-140: Study of the effects of caloric restriction on neurodegenerative conditions

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Numerous studies have shown that the incidence of neurodegenerative diseases increases with age and have made it possible to highlight the genetic bases for some of these diseases. However, how aging induces the establishment of neurodegenerative diseases in genetically predisposed patients remains poorly understood. To study neuronal responses to the combined effect of mutations and physiological conditions, we use C. elegans. This nematode enables us to study neuronal aging through its rapid life cycle, simple nervous system (302 neurons) and its transparency allowing each neuron to be visualized. Moreover, ~70% of genes are conserved between C. elegans and humans, which allows to elucidate universal molecular mechanisms. Our laboratory has shown that structural age-related alterations of the nervous system can be delayed by caloric restriction in C. elegans. This project therefore aims to determine whether caloric restriction also protects the nervous system during pathological conditions using neurodegenerative models in C. elegans. For this, we subject wild-type animals and neurodegenerative models to caloric restriction using eat-2 mutants (which pump less food than normal because of an altered cholinergic transmission from the pharynx), as well as other conditions. These animals will be examined for specific neuronal phenotypes by age-dependent fluorescence microscopy (2, 4, and 7 days adult). Our work will contribute to understanding the mechanisms by which caloric

restriction could prevent neurodegeneration, helping in the diagnosis and treatment of neurodegenerative conditions.

P1-C-141: Investigating motor skill learning impairment in early-stage Huntington Disease mice using an automated home-cage based system

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Understanding the neurological changes underlying motor learning is crucial for making advances in treating movement disorders like Huntington Disease (HD). While many studies in the past have investigated motor skill learning (MSL), few studies have explored these changes in the long term. In this study, we developed a specialized task called PiPaw2.0 to investigate long-term motor skill learning in mice with HD. The task involves the animals pulling a lever and holding it for a required amount of time in order to gain access to water, which is their only source of hydration. The required hold-time for a successful trial in this task was set individually for each animal daily, based on their performance in the previous day, making the task requirements increasingly demanding as animals' performance improved. The animals' behavior during the task is recorded with a video camera and the lever trajectory is recorded using an angular encoder. We assessed the ability of 6-month old male and female wild-type (WT) and HD mice to learn the task over several weeks, measuring their performance 24/7. Results demonstrated that while WT animals showed a steady increase in the average hold-time of the lever, HD mice were unable to adjust to the increasing demands of the task. We observed an increased jerkiness of the pull trajectories in HD mice, as shown by an elevated amplitude of high-frequency movements. The constant change in the required hold-time through the learning process eliminated the habituation process as validated by the lack of change in trial-to-trial correlation, which is an indicator of habit formation and motor variability. Overall, our findings suggest an impairment in fine motor learning and performance in HD mice at an early stage of the disease.

P1-C-142: Inactivation of Cnot3 Elicits Sex-Specific Alterations in Behaviours Relevant for Autism Spectrum Disorders

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social interaction and communication and restricted and repetitive behaviours. There have been significant advances in understanding the disorder's genetic basis, and several identified genes are regulators of protein synthesis. Indeed, several de novo loss-of-function mutations in CNOT3 have been linked to ASD. CNOT3 is a non-catalytic subunit of the CCR4-NOT complex, a deadenylase that destabilizes mRNAs by shortening their poly(A) tail. However, the exact mechanism by which CNOT3 contributes to ASD remains unknown. To investigate the role of CNOT3 on brain development, we generated a forebrain excitatory neuron-specific mutant mouse strain by crossing a floxed Cnot3 with a Emx1-Cre mouse line. No homozygous mice were born; thus, we investigated the effect of Cnot3 haploinsufficiency on ASD-

relevant behavioural phenotypes. Cnot3 haploinsufficient female, but not male, mice presented increased self-grooming behaviour. In addition, Cnot3 haploinsufficient male mice showed social novelty deficits in the three-chamber social interaction test. These findings highlight the contribution of Cnot3 mutations to ASD-related phenotypes.

P1-C-143: One gene to fatten them all: A novel ATGL conditional knockout model for studying fatty acid metabolism in ependymal cells

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Lipid metabolism is a key aspect of brain homeostasis, providing building blocks, signaling molecules and energy. Its deregulation has been observed and investigated in multiple neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. We have previously shown a correlation between lipid droplet accumulation surrounding the lateral ventricles and presence of disease in an AD mouse model and in postmortem human AD brains. These disease-associated lipid droplets are enriched in unsaturated fatty acids (FA), and we found that inhibiting local synthesis of unsaturated FAs rescued periventricular neural stem cell activity and improved hippocampal-dependent learning and memory in AD mice. These data lead us to hypothesize that defects in periventricular FA metabolism contribute to AD-associated neurogenic and cognitive impairments. Here, we begin testing this idea by creating a conditional knockout (CKO) of adipose triglyceride Lipase (ATGL) in FoxJ1+ periventricular ependymal cells. Since ATGL is the primary lipase involved in the initiation of lipoloysis (the release of fatty acids from LD-associated triglycerides), we hypothesized that its deletion would result in lipid droplet accumulation. We indeed find that adult-onset CKO of ATGL in FoxJ1+ cells leads to a striking accumulation of cytoplasmic lipid droplets in brain ependymal cells, with preliminary data suggesting an associated perturbation in periventricular neurogenesis. This novel model provides a system for studying the intimate connection between lipid metabolism in the neurogenic niche and neural stem cell function, as well as for longitudinally investigating the downstream impacts of ependymal cell lipid disturbances on diverse cellular populations and brain function.

P1-C-144: Depressive and anorexic-like outcomes following social isolation and food restriction in female mice.

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It has become well established that communication between the brain and gut plays a major role in many psychiatric conditions, such as depression, anxiety and anorexia. Changes in the gut microbiota and the presence of inflammatory factors in fact, influence neurochemistry and behaviors. Furthermore, stressor exposure (especially social stressors) during sensitive times, such as adolescence and especially in females, may have particularly dramatic long-term consequences on brain-gut functioning.

Collectively, such changes might give rise to depressive symptoms, along with cognitive distortions and inflexibility that fuel the development of destructive coping strategies, such as excessive dieting, rumination and other self-harm behaviors. We sought to model anorexic-depressive like co-morbid pathology using adolescent (3-4 weeks of age) C57BL/6 female mice exposed to a one-month social isolation stressor with or without three weeks of concomitant food restriction, followed by one week of food recovery. As expected, food restricted mice lost considerable weight but returned to normal during the recovery phase. Intriguingly, the social isolation plus food restriction induced signs of anhedonic-like behavior in a modified cookie test that we have created. Similarly, there were some variations in microglial dependent inflammatory, as well as trophic factor signalling in both the gut and brain. However, there were no indications of cognitive inflexibility, as measured using a Y-maze test. These data may have important implications for the development of animal models to capture the complexity of female depression and anorexia, as well as a better understanding of the gut-brain inflammatory and trophic changes that might underpin such psychiatric pathology.

P1-D-145: GPR55 modulates mouse visual function and behavior

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The G protein-coupled receptor 55 (GPR55) is a previously orphan receptor that is mostly activated by lysophosphatidylinositols, but also by endogenous and exogenous cannabinoids. The endocannabinoid ligands and enzymes, as well as the cannabinoid receptor type 2 (CB2) have been shown to play a role in the mediation of murine retina function and visual acuity. To investigate the role of GPR55 in the vision process of mice, we evaluated the differences between knockout mice for the gpr55 gene (GPR55 KO) and their age-matched wild type controls with the C57BL/6J genetic background (GPR55 WT). We used full-field electroretinogram (ERG) of adult mice in light- and dark-adapted conditions to reveal a significant difference between groups for several of its graphical components. We found that scotopic b-wave and photopic a-wave amplitudes are significantly lower in GPR55 KO mice. The first three main oscillatory potentials are also lower in GPR55 mice, as well as the sum of the four main OPs. Furthermore, visual acuity differences during development from P15 to P50 (n=17 mice) were studied by the minimal spatial frequency capable of triggering an optomotor response. The spatial frequency threshold and contrast sensitivity were also measured for adult mice between three and four months old. Developing GPR55 KO mice have a significantly lower acuity before P50 and have the same acuity as GPR55 WT mice for the rest of their life. GPR55 KO mice have a lower contrast sensitivity compared to WT mice. Moreover, GPR55 antagonist, ML-193, diminishes contrast sensitivity when GPR55 agonist, O-1602, increases it. In conclusion, the different components of ERG affected by the deletion of GPR55 show its modulation in different retina cell types that explains the decrease in contrast.

P1-D-146: Gap Junction Delta-2b (gjd2b/Cx35.1) Depletion Causes Hyperopia and Visual-Motor Deficiencies in the Zebrafish

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We provide evidence linking the mammalian connexin-36 (Cx36) ortholog gjd2b/Cx35.1, a major component of electrical synapses in the zebrafish, with a refractive error of eyes in the context of morphological, molecular, and behavioral changes of zebrafish larvae. Two abnormalities were identified. The optical coherence tomography (OCT) analysis of the adult retina confirmed changes to the refractive properties caused by eye axial length reduction, leading to hyperopic shifts. The gjd2b/Cx35.1 depletion was also correlated with morphological changes to the head and body ratios in larvae. The differential expression of Wnt/ß-catenin signaling genes, connexins, and dopamine receptors suggested a contribution to the observed phenotypic differences. The alteration of visual-motor behavioral responses to abrupt light transitions was aggravated in larvae, providing evidence that cone photoreceptor cell activity was enhanced when gjd2b/Cx35.1 was depleted. The visual disturbances were reversed under low light conditions in gjd2b/Cx35.1-/- larvae. Since qRT-PCR data demonstrated that two rhodopsin genes were downregulated, we speculated that rod photoreceptor cells in gjd2b/Cx35.1-/- larvae were less sensitive to bright light transitions, thus providing additional evidence that a cone-mediated process caused the VMR light-ON hyperactivity after losing Cx35.1 expression. Together, this study provides evidence for the role of gjd2b/Cx35.1 in the development of the visual system and visually guided behaviors.

P1-D-147: Anatomical differences across cerebellar neuronal networks in valproic acid-exposed rats

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Cerebellar circuits are involved in the coordination of sensorimotor and cognitive processes crucial for behavior, and they are strongly shaped during neural development and early childhood. Cerebellar differences could impact behavioral changes characterized in many neurological disorders, including autism spectrum disorder (ASD). Despite the increasing prevalence of the disorder, insights into the anatomical differences across cerebellar neuronal networks in ASD remain only partially understood. We aimed to characterize the cerebellar circuitry in a valproic acid (VPA)-exposed animal model of ASD. Rat cerebellar tissues were stained with cresyl violet and captured with a confocal microscope. We examined Purkinje cells (PC) counts and computed their linear density. In addition, we assessed granule cell layer (GCL) thickness across multiple lobules of the vermis and hemisphere. We found that there were: (1) significant losses in PC density in the posterior inferior regions of lobules Crus I, Crus II, paramedian, and copula of the hemisphere, in VPA-exposed rats when compared to controls. We also found that (2) GCL thickness of Lobule 6 was lower, while Lobule 7-8-9 and Lobule 10 were higher in the VPA-exposed rats compared to controls. We were also interested to determine if the linear density of PCs and local GCL thickness would co-vary. We found (3) a significant correlation as well as an alignment of the cross-covariance between the PC and GCL thickness measurements in the lobules of the posterior lobe. Expanding on previous work identifying PC decreases, our lobule-specific analysis indicates that VPA exposure leads to significant alterations in cerebellar cortex circuits, supporting the implication of the cerebellum in autism-related information processing.

P1-D-148: Anatomical clues on how cannabinoids affect visual perception

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From research on developmental and adult plasticity in the rodent brain to the acute and chronic perceptual changes found in cannabis users, the contribution of the endocannabinoid (eCB) system to visual processing is undeniable. Following our series of studies in the retina, we continued to unveil the neural substrates for these cannabinoid-mediated actions in the visual cortices (V1, V2, V4, V5) of the vervet monkey. We used DAB immunohistochemistry to characterize and compare the layer distribution of the CB1 receptor and the anandamide-degrading enzyme FAAH across the different visual cortices. In addition, we compared the expression of these eCB proteins to that of well-known neuronal markers - NeuN, SMI-32, parvalbumin - by double immunofluorescence. CB1R and FAAH had a similar extragranular layer localization across all examined cortices. Besides, CB1R's labelling followed a rostro-caudal gradient, where the lowest levels were found in the primary visual cortex. At the cellular level, CB1R and FAAH showed complementary expression patterns. CB1R was present in axons rich in varicosities surrounding SMI-32-positive excitatory neurons and PV-positive inhibitory interneurons. Conversely, FAAH was found in the somas and proximal dendrites of both these neuronal cell types. These results position the eCB system in a privileged position to integrate higher-order feedback activity to subsequently refine the cortical output. This modulation extends across the visual cortical hierarchy and supports cannabinoids' functional and behavioral effects.

P1-D-149: Investigating performance and lesion-related predictors of motor impairment and recovery following stroke 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. 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, after which performance was monitored for 4 weeks. Performance at baseline, acutely, and at endpoint was compared. Stroke mice had a significantly reduced performance acutely and at endpoint compared to baseline. This reduced performance was explored by dividing the stroke animals into two sub-groups: 1) higher endpoint success and 2) lower endpoint success groups. We found that baseline success, acute success, and acute number of entries into the reaching tunnel were significant predictors of endpoint success. Furthermore, using a semi-automated lesion localization workflow, we were able to find that the percentage of damage in the secondary motor area and in the somatosensory areas was significantly correlated with performance acutely following stroke. Overall, using automated tools like the HASRA for the quantification of post-stroke motor impairments and semi-automated tools for the quantification of

lesion location are essential for investigating potential predictors of stroke recovery and designing effective therapies.

P1-D-150: Studying light-evoked retinal responses following optogenetic vision therapy

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Background: Retinal degenerative diseases are a leading cause of vision loss and rise from the degeneration of rods and cones. Following photoreceptor lost, other cells in the retina remain intact and can be targeted therapeutically with optogenetics. However, the healthy retina sends out ~30 channels of visual information, via different functional types of retinal ganglion cells (RGCs), that each code visual features such as motion, contrast, image size, etc., but due to technical limitations, optogenetics may not be able to restore all of these channels. We aim to systematically assess how many functional retinal channels are restored when opsins are targeted to different retinal cell types. Methods: Experiments are performed in rd1 mice, a model of retinitis pigmentosa, who lose vision by ~P30. We deliver AAVs intravitreally to express MW-opsin in different retinal cells via cell-type-specific promoters. To test whether vision has been restored, we screen mice with a light-room/dark-room test (an arena in which sighted mice show a preference for a dark room). To examine light responses of RGCs, we place retinae on a 256-channel-electrode array and present the retina with a series of movies. Results & Conclusions: We have expressed optogenetic tools in the retina of blind mice and found that their vision is restored (as assessed with the above-mentioned test). We have acquired light responses from WT RGCs and sorted them into functional cell types. We are now working to record restored light responses from optogenetically-treated rd1 retinae.

P1-D-151: Decoding extrinsic and intrinsic sources mediating spiking heterogeneities in vivo

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Understanding how sensory neurons encode incoming information to give rise to perception and behavior has remained a key challenge in system neuroscience. Such understanding is complicated by the fact that neurons ubiquitously exhibit heterogeneities in their patterns of generating action potentials. Despite recent advances in electrophysiological recording techniques and single-cell analysis, the relative contributions of extrinsic mechanisms (e.g., synaptic bombardment) and intrinsic mechanisms (e.g., conductances, cell morphology) towards explaining heterogeneity remain poorly understood. Here we introduce an optimization workflow combined with computational modeling and experimental data to characterize the relative contribution of various factors including morphology, intrinsic membrane conductances, and extrinsic synaptic input in determining spiking heterogeneities in vivo. Specifically, by varying parameters we show that our conductance-based computational model successfully reproduced the highly heterogeneous spiking activities seen experimentally. Then, we performed statistical analysis to quantify which model parameters vary the most to gauge the relative role of extrinsic vs. intrinsic mechanisms. Overall, extrinsic synaptic input was predicted to be the main

factor accounting for spiking heterogeneities. We tested this prediction experimentally by performing pharmacological inactivation of the feedback and applying the neuromodulator serotonin. Our model predicted that feedback inactivation should reduce while serotonin application should increase spiking heterogeneities.

P1-D-152: An integrated Patch-seq atlas of porcine dorsal root ganglion neurons to guide chronic pain research

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The peripheral nervous system transmits pain-related signals via sensory neurons with cell bodies located in the dorsal root ganglion (DRG). While DRG cell types are often investigated by their morphoelectric characteristics, including cell size and electrophysiology, it remains challenging to link this knowledge to the emerging understanding of DRG cell types based on large-scale single-cell transcriptomics. To link molecular and functional characteristics of cell types in the DRG, we collected a multi-modal Patch-seq dataset of 200 cultured DRG neurons from the pig, chosen for its translational relevance as a large mammal. We further collected a parallel atlas of 2189 porcine DRG neurons using high throughput single-nucleus RNAseq (snRNAseq). Following transcriptomics-based integration of our Patch-seq and snRNAseq DRG atlases, we identified 17 cell types, encompassing the major known DRG neuronal types. These cell types include those with pain-relevant subtype defining markers such as SCN10A, SCN11A, TRPM8, NTRK1, TRPV1. By further linking molecular subtypes to electrophysiological and morphological features, we identified hallmark functional characteristics associated with each molecular subtype. In particular, these atlases allowed us to identify molecular subtypes likely corresponding to silent nociceptors and also cold-sensitive neurons. This study provides an unprecedented understanding linking the transcriptomic and functional landscape of the DRG and can be used to derive new molecular targets for specific neuron types involved in pain and sensory processing.

P1-D-153: Time course of target-distractor competition in the frontal eye fields

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When a distractor appears in the visual field shortly before saccade initiation, the resulting saccade trajectory is curved. The magnitude and direction of the curvature is influenced by various factors including distractor processing time. In order to better understand the neural correlates underlying curved saccades and its time course, we recorded from single neurons in the FEF of two rhesus monkeys shifting gaze to a target while an isoeccentric distractor appeared either left or right of the target at various delays after target presentation. Among a sample of visually responsive neurons in the frontal eye field, we found unbalanced patterns of excitatory responses before saccades curved toward or away

from the distractor. This varied with distractor location and processing time. For contralateral distractors, an excitatory visual response was associated with saccades curved toward the distractor, which emerged earlier than the response before saccades curved away from the distractor. For ipsilateral distractors this pattern was reversed--shorter-latency visual response preceding saccades curved away from the distractor and later responses preceded saccades curved towards the distractor. The time of equivalent visual responsiveness was similar for contra- and ipsilateral distractor locations, consistent with a push-pull mechanism across hemispheres controlling the direction of saccade curvature.

P1-D-154: Genetic evidence of the function of Phox2a-expressing anterolateral system neurons in the transmission of chronic pain

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The development of the chronic neuropathic pain state often originates at the periphery, whose abnormal function elicits central sensitization and maladaptive plasticity in nociceptive circuits of the spinal dorsal horn which eventually reach supraspinal areas, bringing about comorbidities such as anxiety and depression. This transmission presumably relies on the function of spinal projection neurons at the origin of the anterolateral system (AS). However, the identity of these neurons and the extent of their functional contribution remain unknown. Here, we asked these questions in the context of the mouse AS neurons that require the transcription factor Phox2a for their normal target connectivity and function in acute nociception. We examined the effects of a spinal cord-specific loss of Phox2a (Phox2acKO) on the development of central sensitization evoked by the spared nerve injury (SNI) model of chronic pain. We found that SNI-treated Phox2acKO mice developed normal reflexive spinal responses in withdrawal behavioral paradigms testing mechanical allodynia. On the other hand, Phox2acKO attenuated the supraspinal responses to cold but not mechanical hyperalgesia, in behavioral paradigms that require the relay of nociceptive information to the brain. Furthermore, Phox2acKO attenuated anxio-depressive-like behaviors evoked by SNI, measured by performance in the open field test and tail suspension test. Our experiments are the first to specifically test the role of AS neurons in chronic pain, without directly interfering with spinal interneurons. Together our data strongly argue that Phox2a AS neurons play an important role in transmitting chronic pain-associated maladaptive plasticity from the spinal cord to the brain.

P1-D-155: Post-ketamine increase in connectivity and gamma power of V1 circuits in the mouse visual cortex

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Oscillations are ubiquitous throughout brain circuits. Gamma oscillations (30-80 Hz) are high frequency brain oscillations that are inevitable for stimulus encoding in anaesthetized and attentional states (Fries et al., 2007). Previously, using multiunit electrophysiology in the cat, we have shown that connected neurons in stimulus-salient (drifting sine-wave gratings) emergent V1 networks exhibited augmented

gamma power and coherence than the unconnected neurons (Bharmauria et al., 2015). Furthermore, recently, we showed that topical application of ketamine -- a non-competitive NMDAR (N-methyl-D-aspartate receptor) antagonist -- leads to vigorous network reconfiguration between mice V1 neurons with higher connections (Ouelhazi et al., 2022). However, the underlying oscillatory mechanisms were not investigated. To this goal, using perievent spectrograms (Bharmauria et al., 2015) between neuronal pairs (n = 38), we revealed two main findings in post-ketamine condition: 1) The baseline power of all oscillations was significantly higher than in the control condition (unpaired t-test, $p < 0.05$). 2) Specifically, neuronal pairs (and ensembles) exhibited significantly higher gamma power in post-ketamine than in control conditions. Overall, these results suggest that ketamine dramatically reorganizes oscillations and stimulus-encoding neural circuits by increasing neuronal connections and background neural noise, thus creating chaos between neurons and impeding stimulus salience/selection. Further, analyses are targeted on spatiotemporal dynamics of these ensembles.

P1-D-156: Anatomical and Molecular Characteristics of VTA Dopaminergic Neurons Projecting to the Forelimb Motor Cortex.

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Background: Learning motor skills is possible thanks to neural plasticity, and dopamine plays a key role in this process. The ventral tegmental area (VTA) is a primary source of dopaminergic neurons, which often co-release other neurotransmitters such as glutamate or GABA. The motor cortex receives projections from VTA, which are essential for motor learning. In this study, we examined the anatomical and molecular characteristics of the VTA dopaminergic projections to the rostral and caudal forelimb motor cortex (RFA and CFA) to gain a deeper understanding of the role of these pathways for forelimb movement. Method: Ten Long-Evans rats received red retrobead injections in RFA or CFA. After one week, the rats were sacrificed to perform immunohistochemistry against TH and/or fluorescent in-situ hybridization (RNAscope) for TH, VGAT, and VGLUT2. Result and conclusion: The results of the RNAscope revealed an important heterogeneity of mRNA for TH, VGAT, and VGLUT2 in VTA neurons projecting to the motor cortex. The combinatorial neurotransmission of dopamine and GABA in these projections suggests a complex signaling mechanism that may play a disinhibitory role in action selection or execution. Our results also show that there are more VTA neurons projecting to the CFA compared to the RFA, but that the ratio of dopaminergic projections is higher in RFA. We suspect that this higher percentage of dopaminergic projections could be related to RFA's specialized role in fine grasp function.

P1-D-157: Distinct mechanisms of visual and sound adaptation in cat V1 neurons

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Sensory cortical regions, considered as unimodal, have the capacity to respond to stimuli outside their basic modality. For example, adaptation to non-preferred orientation in primary visual cortical (V1) neurons, modifies their orientation selectivity (Bharmauria et al., 2022); however, adapting V1 neurons

only to sound also reconfigures orientation maps in anesthetized cats (Chanauria et al., 2019). More recently, it has been demonstrated that sound-induced activity is stereotyped across a low-dimensional space in V1 neurons (Bimbard et al., 2023). Though neurons change their selectivities after visual and sound adaptation, yet their mechanisms are not exactly known. Here, we compared adaptation datasets (neurons) to 12-min of sound (n = 78) and 12-min of visual adaptation (n = 21) in the cat V1. In both cases, neurons exhibited shifts of orientation tuning curves, however, after sound adaptation, neurons showed on average larger bandwidths accompanied with higher firing rates at the flanking orientations, suggesting that the underlying dendritic structure was differentially triggered and recruited in both cases. Based upon previous reports (Jia et al., 2010; Wilson et al., 2016), we speculate that sound modifies the input-output function of neuronal dendrites much more non-linearly than the visual adaptation. Finally, we extend upon our previous dendritic model of 'push-pull' mechanism of acquisition of novel tuning curves (Bharmauria et al., 2022). Overall, these results provide fundamental insights into the distinct mechanisms of plasticity in the sensory cortex.

P1-D-158: Development of small opioids-independent NTS2-selective analgesic compounds with artificial intelligence.

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Chronic pain affects nearly 20% of the Canadian population and is now recognized as a disease by the World Health Organization. Moderate to severe pain is currently treated with opioids which are known to cause various side effects (constipation, nausea, respiratory depression, drowsiness) and strong dependence. A promising alternative is neurotensin, an endogenous neuromodulator peptide which induces analgesia by interacting with its two G-protein coupled receptors NTS1 and NTS2. However, NTS1 activation is also associated with hypotension and hypothermia. Selectivity towards NTS2 is, therefore, crucial. This will be achieved in collaboration with Valence Discovery by exploiting artificial intelligence (AI). 923 patents and 1400 articles have been used to extract chemical structures and biological data of known NTS1 and NTS2 ligands. This data was then used to develop various machine learning models designed to screen a commercial bank of 8 million compounds (MolPort library), predicting affinity and selectivity. These multiparameter algorithms have allowed us to identify 1000 compounds, divided into 12 main families. The best 90 molecules were selected based on their chemical diversity and structural characteristics. Their affinity will first be evaluated with in vitro binding assays. Compounds with an affinity inferior to 1 µM will be tested in vivo in acute, tonic and chronic pain models.

P1-D-159: Head vs body vs world-centered reference frames for encoding translation and rotation in the rostral fastigial nucleus

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Daily tasks such as postural control and reaching rely on estimates of body motion with respect to specific body axes and/or gravity. To contribute to such tasks, head-centered vestibular signals must be transformed into body- and world-centered reference frames. We previously showed that rostral fastigial nucleus (rFN) cells reflect the 3D spatial transformation of otolith signals required to estimate body translation (Martin et al., 2018). However, the extent to which they encode body translation along a specific body axis (body-centered coding) vs. along a particular world axis (world-centered) remains unknown. Similarly, it remains unknown to what extent rFN cells encode rotation about a specific head or body axis, vs. world-referenced estimates of tilt relative to gravity (i.e., computed from transformed canal signals). To address these issues, we recorded rFN cells in 3 monkeys for translation and tilt stimulus combinations and earth-vertical-axis rotations. Cell tuning was characterized with the head and body upright, as well as after static reorientation of the head relative to the body and of the body relative to gravity. Otolith signals on rFN cells ranged from head- to body-centered, whereas canal signals were encoded in complex combinations of head, body and world/gravity-centered reference frames. Importantly, our results show that rFN cells carry true tilt signals and that both tilt and translation estimates reflect a transformation towards body-centered coordinates. However, they also carry complex signal mixtures that may be required for specific tasks.

P1-D-160: Identification of spinal cord networks underlying plastic changes in nociceptive processing

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Capsaicin, the spicy component of chili peppers, is a direct TRPV1 receptor agonist, a key receptor in pain signaling, and is therefore used to model nociceptive processing in humans and animals. In the spinal cord, TRPV1-expressing afferents directly innervate neurons in the superficial dorsal horn. The activation of TRPV1-expressing afferents with peripherally administered capsaicin induces mechanical hypersensitivity and allodynia associated with central sensitization. To investigate the mechanisms of capsaicin-induced central sensitization we sought to develop an ex vivo spinal cord model. Our ex vivo spinal cord model consists of the spinal lumbar explant isolated from adult mice with sensory roots intact. Activation of the afferent terminals was induced by bath application of capsaicin or optogenetic approaches. The optogenetic ex vivo spinal cord model consists of blue light stimulation to the spinal lumbar spinal explant isolated from mice expressing channelrhodopsin (ChR2) in TRPV1 lineage neurons. Neuronal activation was determined by c-Fos expression and quantified by cell counting. Based on the dose-response study, 1 µM is potentially the threshold dose for neuronal activation. In the optogenetic model, there was an increase in neuronal activation in the ChR2 spinal cords compared to wild type. Overall, these data suggest ex vivo spinal cord preparations may be of use for the study of plasticity and sensory network function.

P1-D-161: Spatial dynamics of cholinergic and neuronal activity in mouse visual cortex during resting state and in response to contrast variation.

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The basalo-cortical cholinergic system controls visual function by fine tuning cortical processing. However, dynamics of cholinergic activity during visual experience remains to be defined. To this aim, spatial and temporal ACh release and neuronal activity were compared in gCAMP6s (n=7) or AAV-delivered gACh-3.0 (n=6) mice using mesoscopic imaging in head fixed awake mice . Activities were measured during resting state or in response to contrast variation (bilateral gratings presentation) and the effect of inhibition of ACh degradation by donepezil (DPZ, 0.1, 0.3 or 1 mg/kg, s.c.) was analyzed. Amplitude responses (dF/F) were evaluated at the level of the primary visual cortex (V1), and secondary areas (PM, AL, LM) using Matlab Umit Toolbox, and compared by 2-way ANOVA. Resting state activity was correlated between AL and LM or PM and V1 for both ACh and calcium signals (AChS and CaS). Both correlation ratio were increased by DPZ. There was poor interhemispheric correlation during resting state. AChS and CaS varied in a contrast-dependent manner in all visual areas investigated (V1, AL, LM, PM) ($p<0.0001$) although the variation was smaller in AL and LM and for AChS. Maximal responses were found for 100% contrast in V1 (ACh: 139%; CaS: 187% compared to 30%). The maximal increase in AL, LM, PM ranged from 67 to 320% for ACh and from 137% to 239% Ca. The visual responses from the right and left eyes were similar. DPZ effect was dose dependant. In conclusion, although AChS and CaS changes were spatially and temporally identical, their amplitude was not totally proportional.

P1-D-162: Octave Illusion: how stimulation frequencies modulate perception in musicians and non-musicians

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Objective. The octave illusion is an auditory effect elicited by presenting a dichotic sequence of two tones separated by an octave, with the high and low tones alternating between both ears. To date, few studies have investigated the octave illusion among professional musicians, and they only used the central frequencies of the musical spectrum to elicit the illusion. A recent study from our laboratory suggests that the use of lower or higher frequency pairs can modulate the octave illusion in normal individuals. Whether such modulation is identical in musicians remains undetermined. Our study aimed at investigating how the relative frequency distribution of percepts changes across a larger range of the musical scale in a group of professional musicians in comparison to non-musicians. Method. 30 non-musician adults and 9 professional musicians were presented with 7 pairs of octave-separated frequencies ranging from 40-80Hz to 2000-4000Hz and had to select the choice that corresponded to their perception: 1) A high-pitched sound on the right alternating with a low-pitched sound on the left; 2) A high-pitched sound on the left alternating with a low-pitched sound on the right; 3) A sound that passes from one ear to the other without a change in pitch; 4) none of these answers. Responses were divided in three categories: octave (answers 1 and 2), simple (answer 3) and complex (answer 4). Results. Results suggest differences in the response pattern as a function of the frequency pairs used to elicit this illusion between non-musicians and musicians. Conclusion. The data suggest an impact of musical training on the illusory percept and may help shed some light on the perceptual and neurophysiological correlates of musical training when presented with ambiguous stimuli.

P1-D-163: EVALUATION of tacan as a new target for treating osteoarthritis pain

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Joint pain is the most prominent symptom of osteoarthritis (OA). Patients with OA experience mechanical allodynia which is due in large part to a dysfunction in nociceptors. We previously demonstrated that during OA, mechanosensitive ion channels, which convert high-intensity mechanical stimuli into electrical signals, become sensitized and contribute to mechanical allodynia, where light stimuli are perceived as painful. However, the molecular identity of these channels was unknown, which prevented any progress toward improved pain management in OA patients. We recently identified an ion channel expressed in mouse nociceptors, called TACAN, essential to the sensation of mechanical pain. Here, we examined whether TACAN is necessary to the development of mechanical allodynia in OA. We used behavioural tests to assess primary mechanical allodynia and pain in a preclinical model of knee OA in both male and female mice. We decreased TACAN expression by injecting adeno-associated viral vectors encoding control or TACAN shRNA in the knee capsule. Deletion of TACAN in nociceptors of OA mice significantly decrease mechanical allodynia. In electrophysiology experiments, we characterized the contribution of TACAN to the mechanosensitivity of both mouse and human nociceptors from recently deceased donors incubated with control media or synovial fluid (SF) obtained from OA patients. Mechanically evoked responses are potentiated following a 24h incubation period with OA-SF : mechanically-evoked currents and the percent of active patches are significantly increased. Further investigation will assess whether the inflammatory mediators contained in the SF can lead to the sensitization of mechanical responses in human nociceptors via the TACAN channel and modulate pain symptoms during OA

P1-D-164: Tracing connections of the inner retina to identify circuits resilient to photoreceptor degeneration

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A common form of hereditary vision loss occurs due to degeneration of the light-sensing photoreceptors (PRs), but we know little about downstream changes in retinal circuits. Understanding how inner retinal connections remodel in disease is important for designing therapies that reactivate circuits to restore sight. Here we use the rd mouse models to study the structure and synaptic connectivity of inner retinal circuits in PR degeneration, focusing on the well-characterized direction-selective (DS) circuit. In this circuit, DS retinal ganglion cells (DS-RGCs) receive inputs from starburst amacrine interneurons. In rd mice, I found that the starburst cells remain intact but their density and protein expression may be affected. Currently I am using antibody markers and RNA in situ hybridization to identify DS-RGC subtypes that are affected or resilient in PR degeneration. To analyze the connectivity of this circuit in rd retinas, I am using our TRACR toolkit, which detects retinal cell-cell interactions and connectivity. TRACR

reports trans-synaptic interactions by inducing transcription of a fluorescent reporter in the postsynaptic cell. We have validated that TRACR reliably identifies known circuits in the mouse visual system. I will present ongoing work on applying TRACR in rd mice to analyze DS circuit connectivity following degeneration. Together, these results will identify changes in retinal circuits in degenerative disease, as well as circuit-specific resiliencies to degeneration.

P1-D-165: Influence of neuromodulation on brain state transitions in larval zebrafish

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The simultaneous observation of brainwide activity and behavior in small organisms is revealing how distributed neuronal networks interact to generate behavior. Neuromodulators have been shown to flexibly tune the dynamical properties of circuits to generate different behaviors, but their more general influence on global brain dynamics is poorly understood. Using resonant-scanning two-photon microscopy, we measure spontaneous pan-neuronal calcium dynamics in head-restrained larval zebrafish while monitoring tail movements to investigate how dopamine (DA), norepinephrine (NE) and serotonin (5HT) drive neuronal and behavioral states. We use unsupervised clustering approaches to identify recurrent regional activation patterns, or brain states, which occur spontaneously across all fish and over multiple recording sessions. The regional activation patterns are highly modular and driven by structural connectivity across brain regions, while the probabilities of transitioning between states are conserved across individuals. State dwell times also differ across fish, which allows us to recover their identity over consecutive imaging days. To investigate how neuromodulators might be driving these neuronal states, we use post hoc immunolabeling and image registration to identify DA, NE and 5HT cells in calcium imaging datasets, from which we extract neuromodulatory signaling that correlates robustly with behavior. By combining these approaches with pharmacological treatments, as well as receptor expression profiles inferred from fluorescence in situ hybridization, our goal is to demonstrate a strong spatial and temporal correspondence between mesoscopic brain dynamics and the activity of underlying neuromodulator systems.

P1-D-166: Mistuned harmonic detection threshold unimpaired by missing fundamentals in professional musicians

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The study investigates the interaction of two auditory scene analysis abilities in professional musicians: missing fundamental (F0) perception and mistuned harmonic detection. The missing F0 phenomenon refers to the brain's ability to reconstruct and accurately perceive the pitch of complex tones even when the F0 frequency is missing. The mistuned harmonic detection threshold (MHDT) is a measure of harmonic analysis, which underpins sound fusion and pitch perception. The objective of this study was to investigate the effect of missing F0 on the MHDT of professional musicians to understand the

relationship between musical training and auditory scene analysis. We used the novel adaptive method introduced in our prior study to determine the MHDT in complex tones with present or missing F0. Adult musicians (N=10) were asked to untune the 2nd harmonic of complex tones containing 6 harmonics until they perceived 2 distinct sounds. This task was repeated 5 times to estimate a MHDT. Three tone frequency conditions were used (125, 200, 440 Hz) and MHDTs were obtained with the F0 present and with the F0 missing. The results were compared to non-musician participants. The MHDTs did not vary significantly between the conditions where the F0 was present and where the F0 was missing for the 125, 200, and 400 Hz complex tones. The MHDT of musicians were comparable to the MHDT with present F0 of non-musicians of previous studies. Previous research had suggested that missing F0 may impair auditory scene analysis in non-musicians, but the present results suggest that this may not be the case for musicians. This suggests that musical training may enhance central auditory processing which could have implications for the development of music training interventions.

P1-D-167: Simultaneous stimulation of the left and right cortical representations of the tibialis anterior muscle: a TMS study

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Introduction: Due to its deep location within the interhemispheric fissure, the primary motor cortex (M1) representation of the tibialis anterior (TA) is challenging to target with transcranial magnetic stimulation (TMS). Because the left and right TA M1 are adjacent, it may be possible to target both simultaneously. This study aimed to determine the feasibility of identifying a midline target for both M1 TA that would elicit similar response amplitude bilaterally. Methods: The M1 right and left TA areas of 4 right leg dominant participants (2 males, mean age 25±1 year) was mapped with TMS. Grids were then positioned on the area with the largest responses to find the individual hotspots (i.e., grid location eliciting the greatest response). The bilateral hotspot was found with the same process, recording responses bilaterally. Resting motor thresholds (RMT) were acquired for each hotspot. Recruitment curves (RCs) were derived for both TAs following stimulation of the bilateral hotspot. Results: A bilateral hotspot eliciting similar responses in the right (mean 0.62±0.24mV) and left (0.61±0.17mV) TAs was found in all participants. In 3 participants, RCs on the left and right TAs have a similar shape and amplitude. Bilateral RMT (mean 62±10%MSO) is similar to the left (mean 53±11%MSO) and right (mean 54±12%MSO) TA hotspot RMTs. Conclusions: Our results suggest it is possible to target a midline hotspot resulting in similar responses bilaterally across different stimulation intensities with comparable RMTs. This would be useful in the context of bipedal tasks such as locomotion.

P1-D-168: The effect of attentional allocation on shape processing in the ventral and dorsal pathways

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The two visual pathways model posits that visual information is processed through two distinct cortical systems: The ventral pathway promotes visual recognition, while the dorsal pathway supports visuomotor control. Recent evidence suggests the dorsal pathway is also involved in shape processing and may contribute to object perception, but it remains unclear whether this sensitivity is independent of attentional mechanisms that were localized to the same cortical pathway. To address this question, we conducted an fMRI experiment in which human participants viewed novel objects in different levels of scrambling and were instructed to attend to either the color of the objects or the background. The results showed similar large-scale organization for shape processing along both pathways regardless of the focus of attention. Particularly, in both pathways and across tasks, shape sensitivity increased from early visual cortex to extrastriate cortex but then decreased in anterior regions. These findings support the idea that shape processing relies on a distributed set of cortical regions across the visual pathways, independent of attentional processes.

P1-D-169: Sex Differences of Increased Excitability of the Prefrontal and Motor Cortex to Improve Performance

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Introduction Repetitive transcranial magnetic stimulation (rTMS), has been studied to enhance sports performance,1-4 but sex-differences are not always considered. Differences by sex, like variation in location of commonly stimulated brain regions,5 may impact the efficacy of rTMS as an ergogenic aid. Thus, the purpose of this study is to find if there is a difference in performance by sex in endurance runners following rTMS over the dorsolateral prefrontal cortex (DLPFC), motor cortex (M1), or both regions. Methods Six high level performance runners (3 female) between the ages of 20-41 were included in this study. Runners received one of the following conditions each visit, in a random order: real or sham stimulation over the lower leg area of M1 followed by real or sham stimulation over the DLPFC. Runners then performed a 3k run at maximal capacity. Time per lap and total time were recorded. Results On average men decreased their time by 11.4 seconds (s) and women by 9.1 s after stimulation of both DLPFC and M1 regions. This condition had the greatest percent decrease in time for both sexes (Men M= -1.8%, SD 1.3; Women M= -1.2%, SD=1.5). When targeting one brain region, men had similar results between M1 and DLPFC, while women benefited more from targeting the DLPFC. Conclusions Both sexes saw the greatest improvement in time when both regions were stimulated, but women had twice the percent decrease in time when targeting DLPFC, compared to M1. This suggests that women may benefit more from a cognitive based method, while men may benefit from a motor and cognitive approach.

P1-D-170: Kinin B2 receptor sensitizes the TRPA1 channel contributing to cisplatin-induced neuropathic pain

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Introduction: Cisplatin, an essential chemotherapeutic drug for treating solid tumors, frequently induces neurotoxic side effects such as neuropathic pain. However, effective treatments for neuropathic pain are unavailable. Since the kinin B2 receptor and Transient Receptor Potential Ankyrin 1 (TRPA1) channel have been shown to contribute to the development of chronic painful conditions, we asked if pain induced by cisplatin involves these receptors and if the downstream pathways activated by the kinin B2 receptor sensitize TRPA1 channels. Methods: To this, antagonists and agonists were used to determining these receptors' contribution to cisplatin-induced mechanical allodynia in mice. In addition, we used PLC inhibitor to evaluate the signaling pathway downstream from B2 receptor activation and their effect on TRPA1 sensitization. Results: Kinin B2 receptor and TRPA1 channel antagonists reduced cisplatin-induced mechanical allodynia. Furthermore, local administration of B2 and TRPA1 agonists (all in sub-nociceptive doses) enhanced mechanical nociception in cisplatin-treated mice. Moreover, the PLC inhibitor reduced the increase in mechanical nociception B2 receptor agonist-induced in cisplatin-treated mice. Conclusion: Our results show that B2 receptor stimulation in the cisplatin-induced neuropathic pain model sensitizes TRPA1 through a mechanism dependent on the PLC activation. Thus, regulating this signaling pathway may lead to a novel approach for treating cisplatin-caused painful symptoms and improve patients' adherence to treatment and their quality of life.

P1-D-171: Mechanical Pain Evoked by Single Hair Pulling Relies on Aβ-fiber Conduction and PIEZO2 Transduction.

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Background: We previously published that noxious skin indentation can be signaled by "ultrafast" Aβ high-threshold mechanoreceptors and do not depend on the mechanotransduction channel PIEZO2 in humans. Aim: Here, we investigated the mechanisms of mechanical pain transduction and coding evoked by hair pulling in humans. Methods: To address this, first, we conducted psychophysical experiments by testing a range of pulling forces on single hairs in healthy participants and patients with PIEZO2 deficiency syndrome. We then performed a preferential ischemic nerve block to investigate the contributions of primary afferents to hair-pulling pain. Next, we used in vivo electrophysiological recordings (microneurography) from single mechanoreceptive cutaneous neurons to investigate the neural coding of single hair pulls. Results: We found hair-pulling elicits a distinct, low-threshold pain sensation associated with a specific urge-to-move behavior. Interestingly, patients with PIEZO2 deficiency syndrome had a deficit in pain perception to hair-pulling stimuli. Hair-pulling pain was abolished in the condition of blocked Aβ fibers - a finding confirmed in selective Aβ deafferented patients who did not

perceive hair-pulling stimuli as painful. A class of Aβ high-threshold mechanoreceptors showed selective tuning to painful hair pull stimuli. Discussion: These findings suggest that hair-pulling pain is a specialized ultrasensitive system that relies on Aβ-fiber conduction and PIEZO2 transduction and is encoded by a distinct class of Aβ high-threshold mechanoreceptors in human skin.

P1-D-172: Movement and muscle topography in rat frontoparietal cortex

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A detailed exploration of the brain's control over motor behaviors could help explain the organizational uniqueness in individuals and their ability to learn motor tasks. We and others have shown that long-train intracortical microstimulation (ICMS) in motor cortex (M1) and surrounding fields evokes multi-joint movements resembling natural behaviors (eating, reaching, defense). Motor cortex is also involved in motor learning. Here we present detailed maps of movements and muscle activity evoked from rat cortex. We combine high-resolution ICMS mapping of whole-body topography with electromyography (EMG) to create maps of muscle representation in the frontoparietal cortex. We applied long-train (500 ms) ICMS to M1 and surrounding fields in anesthetized rats while recording video and EMG from up to 16 muscles. ICMS site density was moderately high with as many as 163 sites tested in one animal. Because spontaneous movements are common under light anesthesia, a novel closed-loop system controlled the stimulation timing and parameters using EMG feedback to avoid recording contaminated data. Many ICMS movements were complex and multi-jointed, and some resembled specific behaviours like running/digging. We generated both kinematic and EMG-based topographic maps. We also mapped muscle coactivation in a matrix of all 2-muscle combinations. In some animals, 98% of muscle pairs spanning the head, forelimb, trunk, and hindlimb were coactivated from at least one site. Also, as many as a dozen muscles were coactivated at a single site.

P1-D-173: GABA cell-subtypes and layer specific expression of cholinergic receptors in the mouse visual cortex

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Background: Acetylcholine (ACh) modulates the cortical processing in the primary visual cortex (V1) through muscarinic (mAChR) and nicotinic receptors (nAChR). The control of GABAergic inhibitory circuits is particularly crucial for gating incoming sensory inputs and synchronizing neuronal activities. In order to better understand the muscarinic and nicotinic specific action on these cells, we analyzed their transcriptomic profiles from Allen Institute single-cell RNA sequencing datasets. Methods: The expression of mAChR subtypes (m1-m5) and nAChR subunits (α2, α4, α7, β2) by parvalbumin (PARV), somatostatin (SST), and vasointestinal (VIP) peptide neurons was determined in the different cortical layers using UMAP and dotplots analysis. Results: While m1 was poorly enriched in the GABAergic neurons, m2 expression was particularly strong in the PARV and SST neurons of the infragranular layers.

M3 was found in VIP neurons of the supragranular layers as well as the infragranular SST and VIP neurons. M5 were virtually not found in the GABAergic neurons. α4β2 were expressed as a baseline level in SST and VIP cells but not PARV cells. α7 were scarcely expressed within any subtypes of GABAergic cells. Conclusion: The results reveal a possible specific action of m2 and m3 mAChR in infragranular GABAergic neurons that might modulate cortical output and α subunits in the inhibitory control of V1 through VIP neurons. The lack of specific expression of m1, m5 and α7 receptors on the GABAergic neurons, suggests these receptors are not specifically involved in V1 inhibitory drive.

P1-E-175: Characterizing the encoding of temperature in the median preoptic nucleus and its modulation by fluid balance

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Thermoregulation is tightly interconnected with fluid homeostasis, due to the substantial demands that thermoregulatory effectors (e.g. sweating, panting) place on the body's supply of water. To help animals better cope with the demand for water conservation when experiencing dehydration, thermoregulatory mechanisms are often suppressed, however, how the brain prioritizes fluid homeostasis and adjusts the thermal set point is entirely unknown. The median preoptic nucleus (MnPO) contains key neurons for both fluid and temperature regulation; however, little is known about how these populations interact. To address this question, I have developed a preparation that allows me to simultaneously record single-cell calcium activity from these two populations of neurons using two-photon microscopy while manipulating fluid and temperature balance in mice. To this end, I have been investigating the distinct encoding features of temperature sensing neurons in the MnPO and assessing how fluid balance perturbations affect temperature encoding. Preliminary results suggest that the activation of temperature encoding neurons in dehydrated mice is delayed, suggesting a modulated activation threshold.

P1-E-176: Understanding the dissociative PTSD subtype: Distinct relations between early-life trauma, neuroendocrine, and inflammatory profiles

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A subtype of post-traumatic stress disorder (PTSD) with concurrent dissociative symptoms has recently been identified. However, the underlying neurobiology and unique risk factors for this subtype, such as experiences of early-life trauma, are poorly understood. The current study examined trauma experiences and the relations to inflammatory and neuroendocrine biomarkers among subtypes of PTSD. Participants (N=65) comprised Canadian Armed Forces members and veterans with PTSD, including non-dissociative and dissociative subtypes of PTSD, and healthy controls. Participants completed questionnaires assessing PTSD severity, dissociation, and childhood and lifetime trauma. Cortisol and C-reactive protein (CRP)

were determined via radioimmunoassay and enzyme-linked immunosorbent assay, respectively. Individuals with dissociative PTSD displayed elevated PTSD symptom severity compared to the non-dissociative PTSD subtype. Cortisol levels had strong negative correlations with overall PTSD symptom severity, however, positively correlated with dissociative symptoms, and these correlations were stronger among the dissociative PTSD group. While all individuals with PTSD displayed increased traumatic life exposures compared to controls, only the dissociative PTSD group reported elevated childhood trauma. Specifically, the dissociative PTSD subtype had greater reports of sexual abuse compared to the non-dissociative PTSD group and controls. Moreover, CRP levels strongly correlated to childhood trauma scores among the dissociative PTSD group only. This study highlights distinct relationships between clinical symptomatology, early-life trauma, cortisol, and inflammatory biomarkers between PTSD subtypes, suggesting unique risk factors and biological underpinnings among dissociative PTSD.

P1-E-177: Effects of bisphenol A and bisphenol S on estrogen-sensitive hippocampal signalling cascades, cognition, and anxiety in male and female mice.

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In the mammalian hippocampus, 17β-estradiol (E2) activates rapid non-classical signalling and neurotrophic effects that enhance learning and memory performance. Endocrine disrupting chemicals, like bisphenol A (BPA) may interfere with these E2-mediated signalling and synaptogenic effects. Although many industrial processes have replaced BPA with chemical analogues such as bisphenol S (BPS), our understanding of the bioactivity of these analogs remains unclear. Therefore, we compared the effects of BPA and BPS on these hippocampal signalling mechanisms, neuronal structure, spatial memory, and anxiety. Young adult, gonadally intact male and female CD-1 mice were administered vehicle, BPA, or BPS-containing peanut butter at 4, 25, or 50 ug/kg/day for 10 consecutive days. On day 9, all animals underwent behavioral testing including the object placement spatial memory task and the dark-light anxiety task. Object placement results indicate males treated with 25 ug/kg/day of BPA, 25 ug/kg/day BPS, or 50 ug/kg/day BPS and females treated with 4ug/kg/day BPA, 25 ug/kg/day BPA, and 50 ug/kg/day BPS exhibit impaired spatial memory. The dark-light anxiety results show males treated with 50 ug/kg/day BPS and females treated with 25 ug/kg/day BPA exhibit increased anxiety. Biochemically, bisphenol treatment significantly reduced mkp3 protein expression and increased JNK phosphorylation in the female hippocampus. These findings have important implications for understanding the sexually differentiated mechanisms of bisphenols in the mammalian hippocampus.

P1-E-178: Peripheral inflammatory pain leads to transient stress and inflammatory responses within the male rat hippocampus.

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Stress and inflammation can profoundly affect steroid-sensitive brain regions like the hippocampus. Inflammatory pain can lead to a rise in circulating glucocorticoids that can propagate systemic and neuroinflammatory responses, accompanied by stress-induced decreases in circulating gonadal steroids. Androgens display anti-inflammatory and neurotrophic properties, but the role of androgens in modulating the molecular and morphological changes following inflammatory pain remains unclear. Adult male Sprague-Dawley rats received a hind paw injection of either 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 resulted in no differences in pain sensitivity. By day 10, serum corticosterone and testosterone had returned to control levels. While the circulating steroids appeared to recover, CFA reduced CA3 dendritic branching in a dose-dependent manner. Next, early stress and inflammatory responses following CFA injection were characterized. While serum corticosterone had returned to baseline by 3 days, there was an increase in mean CA3 MKP3 expression. CFA reduced CA3 dendritic branching; however, analysis of astrocyte morphology indicated no change in astrocyte size or the number of projections. While persistent inflammatory pain can lead to dramatic changes within the brain, these results may reflect a more transient response to CFA-induced inflammation. This research provides insights into the mechanisms underlying rapid responses to inflammatory pain.

P1-E-179: Disentangling the depression-suicide relationship among emerging adults: The role of symptom clusters and inflammatory biomarkers

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Background: Suicidal ideation (SI) and attempts (SA) commonly co-occur with depression and are prevalent among young adults. However, not all individuals with depression will develop SI or SA. The current study aimed to identify specific depressive symptom clusters that more closely align with endorsement of SI and SA, and if blood-based biomarkers could disentangle the depression-suicide link. Methods: Participants (N = 539; Mage = 19.4) completed questionnaires including: lifetime and past 12-months SI and lifetime SA, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Depression Anxiety Stress Scale (DASS). To develop symptom clusters, a principal component analysis and cluster analysis were performed with the BDI, BAI and DASS questionnaires. Participants also provided a blood sample for plasma cortisol and C-reactive protein (CRP) determination. Results: Baseline plasma cortisol levels positively correlated with BDI scores, past 12 months SI, and lifetime SA (p's<0.05), while only BDI scores related to CRP (p<0.05). The cluster analysis identified six distinct symptom subtypes, in which past 12 months SI and lifetime SA differed according to cluster (p's<0.001), revealing that suicide outcomes were more frequently endorsed in clusters predominantly characterized by anhedonia, but not neurovegetative or somatic clusters. In contrast, CRP levels were elevated only in the neurovegetative cluster (p<0.001). Conclusions: These data suggest that specific depressive symptomatologies are more strongly associated with SI and SA, and these are not the same depressive features that map onto altered inflammatory biomarkers. The current findings could be used to better identify, prevent, and treat SI and SA.

P1-E-180: GHSR controls food deprivation-induced activation of CRF neurons of the hypothalamic paraventricular nucleus in a LEAP2-dependent manner

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Introduction: The response to prolonged fasting requires the activation of the hypothalamic corticotropin-releasing-factor (CRF)-producing neurons, yet the physiologically relevant neuroendocrine signals that activate these neurons during prolonged fasting are not fully understood. Since ghrelin up-regulates growth hormone secretagogue receptor (GHSR) signaling, and the liver-expressed antimicrobial peptide 2 (LEAP2) down-regulates GHSR signaling, we studied the role of GHSR signaling in the fasting-induced activation of hypothalamic CRF neurons. Methods: We used different pharmacologically or genetically modified mouse models and exposed them to a 2-day fasting protocol. Then we measured body weight, and plasma levels of ghrelin, LEAP2, corticosterone, and glucose. The activation of the CRF neurons was estimated by immunostaining against CRF and c-Fos, a marker for neuronal activation. Results: Fasting resulted in the activation of the CRF neurons, and a rise of the ghrelin/LEAP2 molar ratio. Fasting-induced activation of CRF neurons required GHSR signaling, but not the presence of ghrelin. Finally, we found that preventing the fasting-induced fall of LEAP2 reversed the activation of the CRF neurons in fasted mice and had no effect on body weight or blood glucose. Conclusion: Fasting-induced activation of the CRF neurons involves ghrelin-independent actions of GHSR at hypothalamic level and requires a decrease of plasma LEAP2 levels, suggesting that the up-regulation of GHSR signaling associated with the fall of LEAP2 are physiologically relevant neuroendocrine signals during prolonged fasting.

P1-F-181: Arterial diameter changes in the brain and improvement of olfactory and cognitive functions post olfactory therapy in MCI

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Background: There is a substantial gap between the burden of neurodegenerative diseases and the resources available to prevent and treat them. Research efforts that aim to develop preventive therapies are of ever-increasing importance. Evidence suggests that olfactory therapy may rescue olfactory functions and importantly affect functional connectivity networks and lead to restoration of neural circuits. Method: The aim of our study is to evaluate the olfactory system (olfactory tests and MRI of olfactory brain regions) and cognition levels (cognitive function, episodic memory, executive functions, and language) in control and MCI individuals at baseline, one year later (pre olfactory therapy), and post olfactory therapy. Results: Baseline measurements reveal the presence of deficits in olfaction, odor memory and several cognitive functions in the MCI individuals. Our results also identified medications that impact olfactory function. Furthermore, an increase in average tortuosity of the middle cerebral

artery in MCI was observed and alterations in arterial diameters in the brain compared to controls. In contrast, post olfactory therapy, preliminary data show improvements in olfaction and some cognitive test scores were observed. Differences were also observed in arterial diameters in the brain between pre and post olfactory therapy. Conclusion: Despite extensive evidence showing olfactory system dysfunction is observed in MCI there have been no investigation of olfactory memory, or olfactory training as a therapy. Our goal is to determine if olfactory therapy may provide benefit for individuals with MCI.

P1-F-182: N400 Event-Related Brain Potential Index of Semantic Processing and Two-Year Clinical Outcomes in Persons at High Risk for Psychosis

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Background: The N400 event-related brain potential (ERP) semantic priming effect reflects greater activation of contextually related versus unrelated concepts in long-term semantic memory. Deficits in this ERP measure have been found in patients with schizophrenia and those at clinical high risk (CHR) for this disorder. We tested the hypothesis that in patients at high risk for schizophrenia or a related psychotic disorder, N400 semantic priming deficits at baseline would predict greater psychotic symptom severity and functional impairment after two years. Methods: We measured N400 semantic priming at baseline in CHR patients (n = 47) who viewed prime words each followed by a related or unrelated target word, at stimulus-onset asynchronies (SOAs) of 300 or 750 ms. We measured psychosis-spectrum symptoms using the Structured Interview for Prodromal Symptoms, and role and social functioning with the Global Functioning (GF):Role and Social scales, at baseline, one year (n=30) and two years (n=29). Results: There was a significant interaction between the N400 semantic priming effect at the 300-ms SOA and time on GF:Role scores, indicating that, contrary to expectations, smaller baseline N400 effects were associated with more improvement in role functioning from baseline to year 1, but baseline N400 effects did not predict role functioning at year 2. Conclusions: CHR patients' N400 effects did not predict clinical outcomes over two years, suggesting that this ERP measure may have greater value as a state or short-term prognostic neurophysiological biomarker.

P1-F-184: Getting a handle on rat familiarization: The impact of handling protocols on classic tests of stress in Rattus norvegicus

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Experimenter familiarization with laboratory rodents through handling prior to experimentation is an important practice in neurobehavioral research and is implicated in stress, study variability, and replicability. Unfortunately, different handling protocols have not been thoroughly examined. Determining optimal experimenter familiarization protocols is expected to reduce animal stress and thus improve welfare and data consistency. The impact of different handling protocols was determined through behavioral assessments (i.e. elevated plus maze, light/dark box, open field) as well as via

analysis of fecal boli counts, ultrasonic vocalizations, and blood corticosterone. Male and female Sprague Dawley rats were distributed among three groups: never handled, picked-up, and handled for 5 min once daily over five days. Handled and picked-up rats spent more time in open arms and less time in closed arms of the elevated plus maze and more time in the center and less time at the perimeter of the open field compared to rats that were never handled, indicating that handled and picked-up rats were less anxious than those that were never handled. Male rats consistently defecated more frequently throughout the handling process and throughout behavioral testing, whereas females showed greater concentrations of blood corticosterone. Female rats were found to emit more 50-kHz calls and fewer 22-kHz calls compared to males. The results observed suggest that picking animals up may suffice as a handling method compared to time-intensive handling procedures, and that there are significant sex differences in response to handling.

P1-F-185: Behavioral consequences of conditional Mllt11 knockout in Cux2 expressing cells

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Clinical characterization of autism spectrum disorder (ASD) has identified a broad spectrum of behavioural phenotypes, likely underpinned by a diversity of genetic mutations. The majority of cases present with unknown etiology and heterogeneous behavioural manifestations. Over 100 genes are strong risk factors for ASD thus variability in symptomology may be a result of non-overlapping gene effects between individuals. Core ASD symptoms include social abnormalities, repetitive behaviours, and communication deficits; evidence suggests these can be fractionated according to particular gene and location of disruption. Understanding the behavioral phenotype associated with genes of interest is crucial to individualized treatment development. The protein myeloid/lymphoid or mixed-lineage leukemia; translocated to chromosome 11/All1 Fused Gene from Chromosome 1q (Mllt11) plays a role in the migration and outgrowth of callosal projection neurons (CPNs). Malformation of CPN, resulting in reduced connectivity of the corpus callosum, is a common pathology identified in ASD individuals. We therefore investigated the behavioral consequences of conditional knockout of Mllt11flox/flox in upper layer 2/3 CPNs using transgenic Cux2irescre mice. Tasks designed to reflect core ASD symptoms were performed with both male and female animals. These tests included olfaction habituation/dishabituation, three-chambered social approach, social transmission of food preferences, marble burying, and nestlet shredding. Results indicate sex dependent disruptions in social preference, transmission of food preference, and nestlet shredding in animals lacking Mllt11.

P1-F-186: Environmental enrichment prevents behavioural and blood-brain barrier damage from chronic stress in mice

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Major depressive disorder (MDD) is a leading cause of disability worldwide. Yet, current antidepressants are largely ineffective, likely as they fail to address underlying causes of depression. Chronic stress drives MDD pathogenesis via inflammatory damage to the blood brain barrier (BBB), a highly selective interface of brain endothelial cells connected by specialized tight junctions. Preventing stress-related BBB damage could be a proactive approach to reduce MDD risk. In humans, socioeconomic status is negatively correlated with MDD prevalence, while in mice access to a nest, house, and toy (enriched environment, EE) promotes resilience to chronic stress. However, it is unclear whether these conditions improve underlying BBB damage. Here, we show that access to EE during relevant chronic stress models in male and female mice prevents onset of stress-related behavioural and BBB deficits. First, we used behavioural tests to confirm protective effects of EE against chronic stress in both sexes. Gene expression analysis with qRT-PCR revealed that EE substantially modifies patterns of stress-induced transcription in the BBB, including upregulation of Cldn5, a tight junction protein, and Fgf2, a growth factor, in stressed males. Immunofluorescent staining confirmed Fgf2 upegulation in males but not females with EE after stress. Interestingly, Fgf2 pre-treatment protected a human brain endothelial cell line (HBEC-5i) against TNF-α-induced proinflammatory gene expression and Cldn5 downregulation. Physical exercise (PE) is known to increase Fgf2. We show that exercise preserves Cldn5 expression after chronic stress. Ultimately, this research improves understanding of the relationship between environmental conditions and the BBB in depression.

P1-F-187: The role of AMPARs and their transient exchange in perirhinal cortex for object memory destabilization

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Consolidated memories can be modified through reactivation-induced memory destabilization and subsequent reconsolidation. Previous research indicates that the transient exchange of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) in the lateral amygdala is necessary for destabilizing auditory fear memories in rats; however, the importance of activation and exchange of AMPARs for destabilization of other forms of long-term memory has not been elucidated. Here, we will report our results regarding whether AMPAR activation and exchange from calcium-impermeable AMPARs to calcium-permeable AMPARs via endocytosis is necessary in perirhinal cortex (PRh) for destabilizing object memories in rats. Using the spontaneous object recognition paradigm, we administered bilateral PRh infusions of an AMPAR antagonist, CNQX (0.7µg/µl), immediately before memory reactivation (RA; 24h after initial object exposure); the RA phase was followed by PRh infusions of the reconsolidation blocker, anisomycin. Preliminary results indicate that the pre-RA blockade of AMPARs prevents object memories from destabilizing, thereby rescuing them from the memory deficits associated with the post-RA infusion of anisomycin. We are currently conducting a follow-up experiment evaluating the effects of pre-RA infusions of the AMPAR-endocytosis antagonist, GluA23Y. The results of this research will further establish the loosely understood role of AMPARs in memory destabilization and will accordingly expand our current understanding of the neurobiological bases that underlie the dynamic nature of long-term memory storage.

P1-F-188: Identifying the downstream transcriptional targets that mediate stromalin's effects on synaptic vesicle numbers

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Memory suppressors are genes that limit memory formation. Recently, Stromalin, a member of the cohesin complex (CC), was shown to be a memory suppressor that functioned by limiting synaptic vesicle (SV) numbers in dopamine neurons (DANs) in Drosophila melanogaster. The regulation of SV numbers by Stromalin may be owed to its role in the CC as the CC has been implicated in gene regulation in post-mitotic cells. While SV regulation, function, and SV numbers are critical for learning and memory, there is a gap in our knowledge about the transcriptional regulation of SV numbers. To bridge this gap, a DAN-specific RNA-Seq in DANs with silenced Stromalin was performed to identify the genes downstream of Stromalin that mediate its effects on SV numbers. The identified targets were then subjected to first a primary aversive olfactory memory screen, then a secondary transgenically expressed SV marker [Syt:eGFP] screen to find genes that replicated Stromalin's effects on memory and SV numbers. Five Drosophila genes, Nep1, CG17698, Cox7c, Ttm2 and Su(z)12 were found to be potential downstream mediators of Stromalin's effects, as well as possible novel memory suppressors. We are now testing the hypothesis that CG17698 and/or Nep1 mediate Stromalin's memory suppression effects via limiting SV numbers. We are doing this by characterizing the memory phenotype exhibited by these genes, and will test whether overexpression of these genes can rescue Stromalin knockdown effects on memory. In the future, we aim to unravel the mechanisms of how CG17698 and Nep1 alter SV numbers in neurons.

P1-F-189: Characterizing sec22, a novel memory suppressor gene

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Research over the past several decades has focused mainly on identifying genes that support memory processes. However, recent studies have shown that genes functioning to suppress memory also exist. Through a targeted small scale RNAi memory screen conducted using Drosophila melanogaster, sec22 was identified as a novel memory suppressor. sec22 is ubiquitously expressed and plays a vital role in the transport of vesicles between the endoplasmic reticulum and Golgi apparatus. However, sec22's role in learning and memory is still unclear. Using the aversive olfactory shock assay, we found that knockdown (KD) of sec22 in all neurons, dopamine neurons and mushroom body neurons (MBN), significantly improved memory due to a specific enhancement of learning. The temporal and regional gene expression targeting system is currently being used to determine if this effect is due to sec22's function during development or adulthood. sec22 is part of the synaptobrevin family of genes consisting of the vesicle fusion and secretion associated genes, ykt6, syb, vamp7 and nsyb. KD of ykt6 in the MBN was found to enhance learning while KD of syb, vamp7 and nsyb, impaired it. To elucidate sec22's mechanism of memory suppression, observation of live neuronal function, neuronal anatomy and synaptic communication will be performed. It is postulated that characterizing sec22 as a memory suppressor will

reveal key insights into cellular mechanisms of learning and memory. Moreover, studying memory suppressors may help reveal therapeutic targets for neurological disorders associated with memory loss.

P1-F-190: Assessing motivation to exercise using a wheel running progressive ratio task in rats

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Exercise is beneficial for the body, including the brain. Despite extensive research on the benefits of exercise, little is known about the neural and endocrine mechanisms controlling the motivation for exercise. Wheel running is inherently rewarding for rodents, and calorie restriction increases wheel running in rats. Previous wheel running studies have assessed total rotations run, but this measure fails to distinguish between physical ability and motivation. Therefore, our objective was to develop an operant conditioning task to specifically measure the motivation to run in rats. Adult female rats were calorie restricted (CR) (n=11) or fed ad libitum (AL) (n=12). CR rats were fed to maintain their average weight at 80% of the average AL weight. To gauge motivation to run, we used a progressive ratio task in which rats had to lever press to gain access to a running wheel for 60 s. Brakes were then engaged, and rats were required to lever press again to regain access. The number of presses required to access the wheel increased with each successive ratio completed. If the rat failed to reach lever press criterion after 10 min, the task ended. The last ratio not completed was considered to be the rat's breakpoint. CR rats completed significantly more rotations per session than AL rats throughout the task. Importantly, CR rats also had a significantly higher breakpoint than AL rats, indicating that CR rats had a greater motivation to run. This progressive ratio task is a novel tool for studying the neural and endocrine mechanisms driving the motivation to exercise in rats.

P1-F-191: Appetitive associative learning & memory: A new fish model in behavioral neuroscience with Mikrogeophagus ramirezi

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Despite the numerous sophisticated behavioral tools created for, and genetic tractability of the zebrafish, there is growing evidence that the zebrafish may not be the most suitable species for learning & memory tasks employed in neurobehavioral research. Their proneness to exhibiting fear and anxiety-like behaviors paired with their innate preferences for staying in a social group often make implementing sensitive learning tasks difficult. The present study examines whether the German ram cichlid can perform an appetitive learning task. German ram cichlids were able to show a reversed preference for the color green, which was the least preferred color in a color preference task, after training with a food reward. This suggests that adult German ram cichlids have the behavioral plasticity to override natural environmental preferences when provided sufficient motivational rewards and provides a new, easily adaptable model for neurobiologists interested in studying cognitive function with fish in the laboratory.

P1-F-192: Sidekick-1, a novel regulator of stress resilience in the prefrontal cortex

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Stress is a major risk factor for depression, yet some individuals are resilient to stress. Both environmental and genetic factors contribute to neural circuit dysfunction in depression and genes that regulate the formation, maintenance, and plasticity of synapses are of particular interest as molecular hubs for regulation of circuit function. We previously identified Sidekick-1 (Sdk1) as an affective circuit hub gene in a network regulating stress resilience and overexpression of Sdk1 in the prefrontal cortex (PFC) increased resilience to stress in male mice. Separately, several genome-wide association studies in humans found SDK1 variants associated with depression, suggesting an evolutionarily conserved role in regulation of emotional behavior. Sdk1 is a cell surface molecule implicated in circuit formation in the developing retina. However, little is known about cell-specific expression patterns of Sdk1 in the adult brain and its function within affective circuits. In this study we found that Sdk1 is modulated by chronic stress in a sex-specific manner and is expressed in subsets of both excitatory and inhibitory neurons, with a significant enrichment in deep layers of the PFC. Cell-type and cortical layer specificity was conserved between mice and humans. We used the probabilistic reversal learning task to probe reward learning in animals where prefrontal Sdk1 expression is altered. Future work will address the circuit-specific effects of Sdk1 in behavioral adaptation to stress. Understanding how Sdk1 confers resilience may lead to development of new mechanistically-informed treatments for depression.

P1-F-193: Impact of chronic stress on blood-brain barrier development and stress response in adolescence

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According to WHO, major depressive disorder (MDD) is the first cause of disability worldwide with a prevalence at 3-8% in adolescents. Unfortunately, around 40% of depressed adolescents do not or respond poorly to available treatments suggesting that causal mechanisms remain untreated. Chronic stress is an important risk factor to the development of MDD and it is associated with increased peripheric inflammation during adolescence. A prolonged rise in inflammatory molecules circulating in the blood can damage the blood-brain barrier (BBB), a highly selective barrier protecting the brain. Intriguingly, adolescents suffering from MDD have elevated plasma levels of markers associated with BBB permeability. Since adolescence is a critical time window for neurovascular development and maturation of the BBB, I investigate how chronic stress exposure impact it. To do so, I take advantage of an emotional stress paradigm, witness chronic social defeat stress, which induces susceptibility or resilience in adolescent male and female mice as measured with anxiety- and depression-like related behavioral tests. I explore the effects of stress responses on the neurovasculature by assessing expression of genes linked to BBB integrity and function. Transcriptomic profiling will be complemented by immunostaining and morphological analysis. Deciphering stress-induced neurovascular alterations occurring during

adolescence could allow a better comprehension of the biological mechanisms that underlie the development of depression in this understudied population.

P1-F-194: The trisynaptic and monosynaptic pathways encode memories in parallel with different levels of specificity

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The entorhinal-hippocampal system is crucial for memory and consists of both the trisynaptic and monosynaptic pathways. The specific role of each is poorly understood, but it has been suggested that they operate in parallel with the trisynaptic pathway encoding specific details and the monosynaptic pathway encoding features common between events. The prolonged development of the trisynaptic pathway may also be linked to the phenomenon of infantile generalization. We predicted that silencing the trisynaptic pathway would reinstate a juvenile-like state of memory generalization and that allocating a fear memory to the monosynaptic pathway would allow for the activation of a non-specific fear memory. Here we use a circuit-specific optogenetic approach to selectively silence or activate each pathway during contextual fear conditioning. We found that the trisynaptic pathway supports context specific fear memories while the monosynaptic pathway encodes non-specific memories. This supports the claim that both pathways operate in parallel and encode memories at different levels of specificity.

P1-F-195: How real is virtual reality? Comparing eye-hand coordination in VR and real world object interactions

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We translated an object interaction task from the real world (Lavoie et al., 2018) into VR to test how visuomotor behaviours change from real to virtual environments. First, we showed that participants in VR change their hand and arm movements to accommodate the virtual body being visualized (Lavoie & Chapman, 2021). Movement changes were correlated with an increase in feelings of ownership over the limbs. Here, we compare the similarities and differences in eye-hand coordination between 3 virtual versions of this task, with varying levels of haptic feedback, to a real-world version. In this task, participants move a box of pasta between 3 shelves in a specific sequence, repeated at least 20 times. Participants moved slower in VR compared to the real world, but of the VR conditions, participants moved fastest when true-haptic feedback was provided to their hands. As well, compared to real-world behaviour, participants spent more time visually fixating their virtual limb immediately prior to, during and just after moving the box. But, again, in the true-haptic VR condition, participants' eye-hand coordination gravitated closer to their behaviour in the real world. The minimal haptic feedback provided to the participants in the no-haptic feedback VR condition showed results consistent with prosthetic participants performing this task (Hebert et al., 2019), who also lack haptic feedback. Finally, we show that, apart from these differences, participants completing the task in VR exhibit similar timing and relative duration of fixations to objects and targets as their real-world counterparts. Taken together,

this study shows that eye-hand coordination in VR and the real world are quite similar, but haptics remains an important hurdle to increase VR authenticity.

P1-F-196: Uncovering novel pathways that control learning and forgetting through regulation of dopamine receptor trafficking

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Memory flexibility, the ability to both learn and forget, is an essential feature of the brain. Dopaminergic signaling through two receptors, Dop1R1 and Dop1R2, which are highly expressed in the memory center of Drosophila melanogaster, are critical for learning and forgetting, respectively. However, it remains unclear how these receptors are trafficked to and from the cell membrane and how changes in trafficking impact the ability to learn or forget. To advance our understanding of Dop1R1/2 signaling, we utilized TurboID proximity labeling proteomics and RNAi screening to identify Dop1R1/2 interactors that regulate memory. Proximity labelling in cell lines expressing Dop1R1/2-Turbo-V5 constructs identified candidate proteins significantly more abundant around one or both receptors. Disruption of candidate proteins in mushroom body (MB) memory circuits leads to significantly altered memory functionality. Several candidates are predicted to either transport GPCRs to or remove from, the plasma membrane, including the Sec24AB COPII protein, predicted to bind and transport GPCRs from Endoplasmic Reticulum to Golgi. Interestingly, loss of Sec24AB decreases memory formation while increasing stability. Immunostaining and in vivo imaging experiments will reveal if these candidates change Dop1R1/2 receptor expression at synapses, downstream secondary messenger signaling, and synaptic memory trace formation/stability. Altogether, our study will identify and characterize novel pathways regulating dopaminergic signaling and illuminate how the brain genetically fine-tunes memory.

P1-F-197: The effects of multimodal distractors on bottom-up attention

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During Pavlovian conditioning, Sign-Tracker (ST), Goal-Tracker (GT) and Intermediate (IG) phenotypes emerge. They are characterized by the degree to which they tend to attribute incentive salience to cues associated with rewards. Research has shown that these phenotypes also differ in other aspects. For example, in humans, STs tend to favor bottom-up while GTs tend to favor top-down attention. Some researchers have found the same pattern in rats. However, the evidence is limited. Therefore, it is hypothesized that if the addition of a distractor increases the difficulty of the task, then the performance will decrease when distractors are added compared to the absence of distractors. It is also hypothesized that if STs favor bottom-up and GTs favor top-down attention, then light and auditory distractors will particularly affect the performance of STs in a sustained attention task (SAT). This study evaluates the signal detection performance of rats during nine different SAT with distractors. The sample was 86 Long-Evans rats. Findings show a main effect of distractors, but no clear effect of phenotypes in detection performance. These results support that adding distractors increases the difficulty of the task but

negates that the performance of STs is more affected, suggesting that distinction between phenotypes in terms of attention capacity is less important than previously presented. This study nuances the current findings and highlights the importance of future studies to clarify the use of bottom-up attention phenotypes. Authors declare no conflicts of interest.

P1-F-198: Early-life adversity alters blood-brain barrier gene expression in mood-associated brain regions

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Early-life adversity (ELA) events can set a specific vulnerability threshold for future stress events precipitating non-adaptative emotional responses. Indeed, ELA can improve or impair the ability to cope with stressful situations. ELA has been described as a risk factor for the development of depressive- and anxiety-like behaviors. Additionally, the loss of blood-brain barrier (BBB) integrity has been implicated in affective disorders, such as depression, which can arise from chronic stress, and its permeability has been found to be differentially modified in mice exposed to chronic social defeat stress (CSDS). Male and female mice were exposed at post-natal day10, to a 10day ELA period of maternal separation and limited bedding/nesting, then subsequently subjected to 10day CSDS at week 8. 24 h after the last defeat, the stress response was tested with a social interaction test and the elevated plus maze. Punches from brain areas regulating reward, mood, and emotions were collected for qPCR analysis. Surprisingly, ELA did not exacerbate vulnerability to stress, in fact, it increased the expression of the stress-resilient phenotype. Transcriptomic profiling of the BBB revealed diverse patterns of gene expression associated with ELA and an association with CSDS, as well as sex-specific alterations. These results support that ELA could modulate stress responses when facing emotional events in adulthood, possibly through long-lasting changes in BBB integrity.

P1-F-199: Optogenetic manipulation and 1-photon calcium imaging of an anomalous pyramidal cell type in the subiculum reveals sustained cellular activity and robust responses to novelty

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Introduction: This research investigates a unique excitatory cell type, termed "deep cells", that sit in the deepest layer of the subiculum. 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 and optogenetics 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 and perturb deep cells during behavior. During these experiments, I use wire-free 1-photon miniscopes to image cellular activity and optogenetics to excite deep cells while mice undergo novel object recognition assays. Results: Imaging data 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 24-hours later, this phenotype persisting even 100 days after initial introduction to an object. The optogenetic stimulation of deep cells caused disruption in novelty recognition with mice favoring familiarity over novelty on the novel object recognition test, indicating that deep cells can play a pivotal role in effective novel object recognition processes. Conclusion: Our work here reveals a novelty-driven cell type that operates on behavioural timescales, which can causally control novelty-driven behaviour.

P1-F-200: Striatal circuits for auditory decisions

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The ability to use sensory information to guide decisions is a core cognitive ability. In rats, inactivation of two distinct subregions of the dorsal striatum, the anterior dorsal striatum (ADS) and the tail of the striatum (TS), impair performance in tasks requiring accumulation of auditory evidence. While this demonstrates that multiple striatal pathways are required for auditory decisions, what distinct role these pathways play is not known. To directly compare the role of striatal subregions during auditory decision making, I carried out a detailed survey of encoding in single neurons using high-yield silicon (Neuropixels) probes implanted at four sites spanning the anteroposterior striatal axis. Rats performed the "Poisson Clicks" task, in which they were presented with two competing streams of auditory clicks from a left and right speaker. To receive reward, the rat had to orient to the side that played the greater number of clicks. We found that the most anterior neurons tended to have long-lasting, side-selective responses to the individual evidence pulses, consistent with the gradual accumulation of evidence favoring a choice. The most posterior neurons, by contrast, tended to respond strongly, but transiently, to the individual evidence pulses. Using simultaneous recording of both regions, we found that the value of accumulated evidence encoded in the ADS neuronal population could be predicted better from simultaneously recorded TS population spiking than from the experimenter-defined stimulus itself. This suggests that TS may represent the internal sensory signal that is accumulated by the brain. These results demonstrate a previously unknown subcortical circuit architecture for perceptual decisions involving multiple, interacting basal-ganglia loops.

P1-F-201: The synaptic adhesion protein Neuroligin-2 shapes vigilance state duration and quality under both baseline and sleep deprived conditions

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Improper sleep hygiene negatively impacts health in mammals. To improve sleep duration/quality, greater understanding of the underlying regulatory mechanisms is needed. Vigilance states are modulated by different neurotransmission systems through changes at the synaptic level involving, amongst others, synaptic adhesion molecules such as Neuroligins. Our group found that the knockout (KO) of Neuroligin-2 (NLGN2), which regulates inhibitory transmission, reduces time spent asleep in male

mice under baseline (BL) conditions. Nlgn2 KO mice also have more electrocorticographic (ECoG) delta activity (1-4 Hz) during slow-wave sleep (SWS), a brain oscillation involved in memory and strongly responding to sleep deprivation (SD). We here investigate which properties of individual slow waves (SW) could explain this increase in delta activity. We also verified the response of Nlgn2 KOs to SD. Adult male Nlgn2 KO mice and wild-type (WT) littermates underwent ECoG electrode surgical implantation, then were recorded for 24h of BL, 6h of SD, and 18h of recovery. Our data shows that Nlgn2 KOs have greater SW density and amplitude, indicative of higher SW generation and cortical synchronization. Furthermore, KO mice have altered SD response including accelerated PS recovery. We are now testing whether similar phenotypes can be observed in females and if viral manipulations of Nlgn2 expression at the adult stage can also modulate vigilance states. First analyses support both hypotheses. Overall, our work uncovers a role for NLGN2 in shaping vigilance states under both BL and SD conditions.

P1-F-202: Serotonergic modulation of ventral hippocampus underlies sex-related differences in anxiety

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Anxiety disorders are among the most common psychiatric conditions worldwide, with women being almost twice more likely than men to be diagnosed with an anxiety disorder throughout their lifetime. Serotonergic (5-HT) neurons from the median raphe (MnR) are heavily involved in the regulation of mood and anxiety, yet the neural substrates underlying sex-related differences in anxiety are still largely unknown. The ventral hippocampus (vHP), a region that has been described as a major modulator of anxiety through oscillatory communication with other brain areas, receives dense 5-HT inputs from the MnR. We hypothesized that vHP-projecting 5-HT neurons are instrumental in controlling anxiety. Using a combination of pathway-specific optogenetic activation and local field potential recordings in mice of both sexes, we observe that cell-type specific activation of MnR serotonergic neurons alters theta oscillations in the vHP. Strikingly, excitatory opsin ChR2 mediated optogenetic activation of these projection neurons robustly increases anxiety levels in a sex-dependent manner, with female mice showing increased anxiety in a battery of previously validated anxiety tests. This work shows that 5-HT release in the ventral hippocampus directly increases anxiety and associated changes in oscillation properties. Together, these results provide a novel mechanistic insight into a previously under-investigated sexual dimorphism in the raphe-ventral hippocampus serotonergic pathway, thereby paving the way for new therapeutic avenues for the treatment of anxiety disorders in females.

P1-F-203: Disrupted spike dynamics of dorsal CA1 excitatory and inhibitory neurons during sharp wave ripples in the TgCRND8 mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is a progressive neurological disease associated with the decline in episodic memory. Critical for memory consolidation, sharp wave ripples (SWR) are transient bursts of oscillatory activity (150-250 Hz) in the hippocampus that occur during slow wave sleep and awake rest. Although abnormal SWRs parallel memory deficits in several mouse models of AD, the corresponding deficits at the single neuron level remain unknown. Here, we used an array of wire electrodes to record neuronal activity from the dorsal hippocampal CA1 of 3-month-old wildtype (WT) and TgCRND8 mice with AD-related amyloidosis. From the signals recorded during sleep, the spiking activity of individual neurons was isolated and further classified into putative pyramidal neurons and interneurons based on spike waveforms and temporal patterns. We found significant decreases in firing rates of putative interneurons during baseline and SWR events in the TgCRND8 mice, while firing rates of putative pyramidal neurons were unaffected. Also, in WT mice, both neuron types preferentially fired at a specific phase within each oscillatory cycle of SWRs. In the TgCRND8 mice, however, most pyramidal neurons lost the phase preference, firing at various phases with reduced phase-locking strength. In contrast, despite decreasing firing rates, interneurons appeared to maintain phase-locked firings. Our observations suggest that early-stage amyloidosis affects distinct features of spike dynamics of hippocampal pyramidal neurons and interneurons, leading to disrupted spike coordination during SWRs.

P1-F-204: How does neuronal activity of 5-HT - ventral hippocampus pathway change during exploration of aversive environments?

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In the brain, serotonin (5-HT) and the ventral hippocampus (vHP) are two main modulators of anxiety- and fear-related behaviours. The vHP is densely innervated by serotonergic fibers but the precise mechanisms through which 5-HT - vHP pathway is recruited and how its activity in relation to aversive stimuli remain to be characterized. This study aims to investigate how the activity of 5-HT neurons that project to the vHP changes, at the population level, to adapt to aversive contexts in male and female mice. A retrograde viral vector was infused in the vHP of SERT-Cre mice to enable conditional expression of the calcium sensor GCaMP6s in vHP-projecting 5-HT neurons. An optic fiber was implanted above the raphe to perform fiber photometry recordings during exploration of aversive environments. We analyzed concomitant changes between vHP-projecting 5-HT neurons activity and exploration of anxiogenic contexts. Our results suggest that the activity of the 5-HT - vHP pathway is increased during exploration of an aversive environment and covaries with specific behavioral epochs. In particular, vHP-projecting 5-HT neurons activity seems to be modulated during risk assessment. Altogether, our results provide a deeper insight into the neuronal circuits underlying emotional behaviours to adapt to aversive situations in male and female mice.

P1-F-205: Chronic stress alters reward-related decision-making in the PFC in male and female animals

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Depression is a debilitating psychiatric disorder marked by impaired reward processing, or anhedonia. Gaining insight into neural mechanisms of reward processing in healthy and disrupted states will increase our understanding of the mechanisms of depression. The prefrontal cortex (PFC) plays a major role in reward processing and decision-making, and structural and functional alterations are observed in depressed patients. Furthermore, in humans with depression, impaired reward processing in a probabilistic reversal learning task (PRL) is associated with decreased reward signal magnitude and PFC connectivity. While human studies are critical in identifying potential depression-relevant circuits, translational rodent studies are essential to establish causality and define precise molecular and circuit-level mechanisms. As stress is the leading risk factor for depression, rodent studies using chronic social defeat stress (CSDS) are commonly used to model depression-like behavioral alterations although the translational relevance of specific mouse behaviors is not always clear. To bridge this translational gap, we examined how CSDS alters reward-related decision-making and the neural signatures of reward in PFC using in vivo single photon calcium imaging during PRL before and after stress. Using reinforcement learning to model behavior, we demonstrate that CSDS modulates parameters of learning and the corresponding neural signatures.

P1-F-206: A novel protocol for simultaneous appetitive and aversive associative learning in male and female mice

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The affective valence of a stimulus ranges from appetitive (positive) to aversive (negative). Valence representations infuse stimuli with emotional significance that powerfully regulates approach and avoidance to shape behavior. Appetitive and aversive stimuli can be thought of as opposing ends of a valence spectrum. However, they are primarily studied in isolation preventing direct comparison that is necessary to determine unique and shared neurobiological underpinnings. Here, we developed a classical conditioning paradigm, in which mice are simultaneously trained to associate three distinct auditory cues to a positive, negative or neutral outcome. We find that both male and female mice acquire robust appetitive and aversive associations over 14 days of training. Conditioned behavioral responses remain stable across three days of extinction. We further explored interindividual behavioral heterogeneity using machine learning approaches to profile common and distinct behavioral repertoires. Finally, using in-situ hybridization we confirm that in the nucleus accumbens, a key region implicated in valence processing, both types of medium spiny neurons, dopamine receptor D1- and D2-expressing, respond to both appetitive and aversive conditioned stimuli. Our novel dual-valence classical conditioning protocol provides a validated behavioral paradigm that can be used to probe mechanisms of disease-relevant disturbances of valence processing in male and female mice.

P1-F-207: The lateral habenula signals aversive-predicting cues to the dopamine center

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Learning to adapt behavioral responses to threatening or unpleasant events is essential to maximize survival. The lateral habenula (LHb) is a small nucleus of the epithalamus receiving neural inputs from the basal ganglia and limbic system, and in turn sends neural projections to the dopaminergic ventral tegmental area (VTA). It is then ideally positioned to integrate affective signals into the selection of action. In this project, we test the hypothesis that VTA-projecting LHb neurons encode aversive signals involved in associative learning to promote escape behavior. Specifically, we use an intersectional viral approach to direct expression of the genetically encoded calcium sensor GCaMP6s specifically in VTA-projecting LHb neurons to monitor their activity using fiber photometry calcium imaging in freely moving mice during an active avoidance task. In this protocol, mice learn to associate a neutral stimulus (tone) with an upcoming mild foot shock, which is required to engage either escape or avoidance responses. We have observed that neuronal activity of VTA-projecting LHb neurons increases when mice are presented with an aversive airpuff or mild foot shocks, confirming their role in encoding aversive signals. Moreover, we found that an auditory cue (tone) paired with a foot shock progressively causes cue-driven activity in VTA-projecting LHb neurons during avoidance learning, which is not observed when tone is not contingent to foot shock (unpaired). Taken together, these findings suggest that VTA-projecting LHb neurons encode aversive signals and cues predicting them, and that they may be involved in the associative learning to promote defensive escape behaviors.

P1-F-208: The mechanism of corticotropin-releasing hormone in the medial prefrontal cortex in stress-induced working memory deficits in mice

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Corticotropin-releasing hormone (CRH) is widely known as a hormone that mediates stress responses via hypothalamus-pituitary-adrenal axis (HPA axis). Besides its neuroendocrine release, CRH is also expressed and acts across various brain areas including the medial prefrontal cortex (mPFC). Previous studies have shown that in the mPFC, CRH-CRHR1 signalling regulates stress-related behavioural and cognitive changes. Recently, using the trial-unique non-match-to-location (TUNL) task to measure the spatial working memory in mice, our group showed that 4-hour restraint stress impaired working memory, and that pharmacological blockade of CRHR1 in the mPFC prevented the stress-induced impairment. However, it remains unknown how stress affects the CRH-CRHR1 signalling in the mPFC with relevance to spatial working memory. We hypothesized that stress activates mPFC CRH neurons and drives their CRH release to signal on CRHR1. We first confirmed that the CRH neurons in the posterior, but not anterior mPFC are activated after 4-hour restraint stress by using immunofluorescence for cFos. Next, by using fiber photometry in freely behaving mice, we monitored mPFC-CRH neurons activity (GCaMP6s is expressed in CRH neurons) and CRH dynamics (a newly developed CRH sensor GRABCRF is

expressed in the mPFC) during 4-hour restraint stress and TUNL task. This study will help us understand how CRH system in the mPFC mediates stress-induced working memory deficits.

P1-F-209: Identifying unique cell types and molecules involved in fear memory

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Following a traumatic event, some individuals experience adverse and persistent psychological symptoms, resulting in post-traumatic stress disorder (PTSD). To better understand this disordered type of memory, we must first understand the cells and molecules involved in experimentally well-controlled models of fear memory, so that effective interventional strategies for PTSD can be developed. Our research has shown that classic "textbook" cell types of many brain regions can be divided into distinct subtypes based on the genes they express. Here, we sought to identify the unique subtypes of cells participating in the creation and recollection of fear memories in the mouse subiculum. We assayed cell-type transcriptomic changes following fear memory using a mouse line allowing for the tagging of cells active during a given time window. Using a combination of single cell RNA sequencing and multiplexed in situ hybridization, we investigated the cell-type-specific participation and gene expression patterns arising from exposure to a fear-associated environment, relative to both a novel environment and a home cage environment. We revealed unique cell types in the ventral subiculum that preferentially participate in fear memory. Furthermore, we uncovered unique transcriptional signatures of memory, thus elucidating cellular and molecular targets related to fear memory. These findings provide a vital framework for future experiments investigating the therapeutic relevance of these targets in interventions for PTSD.

P1-F-210: Median raphe glutamatergic neurons activity in relation to vigilance state and modulation of hippocampal rhythms

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Two distinct hippocampal rhythms are highly involved in memory consolidation: theta occurring during REM sleep and sharp-wave ripples occurring during non-REM sleep. Manipulation of the median raphe activity modulates both hippocampal rhythms. The median raphe contains diverse neuronal populations including hippocampus projecting glutamatergic neurons expressing the vesicular glutamate transporter type 3 (VGLUT3). The exact contribution of the median raphe VGLUT3+ neurons to hippocampal activity is still unclear. In this study, we aim to characterize median raphe VGLUT3+ neuronal population activity in relation to hippocampal activity. To target median raphe VGLUT3+ neurons, we injected Cre-dependent viral vectors in VGLUT3-Cre mice allowing for specific expression of calcium sensors and optogenetics tools in our population of interest. First, we assessed median raphe VGLUT3+ population

activity in relation to hippocampal activity across sleep-wake cycles. To do so, we used simultaneous electrophysiological recordings in the hippocampus with fiber photometry recordings in the median raphe. We observe that VGLUT3+ neurons are highly active during wake and REM sleep, vigilance states with high hippocampus theta activity. Next, we optogenetically activated glutamatergic neurons during different vigilance states to assess their potential to modulate hippocampal rhythms. We show that activation of VGLUT3+ neurons during non-REM sleep suppresses sharp-wave ripples and strongly modulates theta oscillations during REM sleep, suggesting a role in memory consolidation.

P1-F-211: Effects of acute ethanol exposure and handling on the behavior of juvenile zebrafish

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The zebrafish is a model organism employed in numerous subfields of biology due in part to its well documented behavioral repertoire and evolutionary conserved features. For example, the zebrafish has been successfully employed in modeling alcohol related disorders. Several studies have demonstrated that acute exposure of juvenile zebrafish to low dose alcohol can lead to significant concentration dependent alterations in behaviour. However, most behavioral paradigms with zebrafish include human handling that can lead to elevated fear and anxiety, an often overlooked but potentially important confound. Furthermore, handling is highly variable and can thus reduce replicability and reproducibility of results. Here, we explore the potential interactive effects of acute ethanol exposure and handling stress on juvenile zebrafish behavior. At age 7 dpf, three acute ethanol concentrations (0%, 0.5% and 1 %) and two handling procedures (fish transferred by pipette from their home well plate to a new well plate and fish remaining in their home well plate) were employed, a 3x2 between subject design. Subsequently, swim path parameters of the zebrafish were recorded for 20 minutes. Significant 'alcohol x handling' interaction was found in intra-individual variance of distance to centre and in high-mobility cumulative duration & frequency. This study illuminates the potential need to consider handling procedures with juvenile zebrafish and the impact it may have in acute alcohol exposure paradigms.

P1-F-212: Inferring working memory capacity following acute Cannabis smoke exposure in rats: the case for automated quantification approaches in preclinical drug testing

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Working memory capacity (WMC) refers to the amount of information that is held in WM and is utilized for higher cognitive functions. Human WM may be impaired by high- Δ9-tetrahydrocannabinol (THC) Cannabis exposure, but the effect of cannabidiol (CBD) is less known. Here, we present a novel, spontaneous behavioural task measuring WMC in rats with either objects or odours. Stimuli are shown in groups of 6 identical or 6 differential items, for low- and high-cognitive loads, respectively. Traditionally, WM tasks require a long training period, learned rules, and may evaluate qualities like recency instead of WM-based recognition. In contrast, our new WMC task relies on rodents' innate

novelty seeking behaviour, as shown by preferential interaction with a novel stimulus after a delay. Additionally, we present a novel, human-machine hybrid (HYB) behavioural quantification approach which supplements stopwatch-based scoring with supervised machine learning-based classification. Using the novel WMC task and HYB method, the impact of acute exposure to high-THC or high-CBD Cannabis smoke was evaluated. Under control conditions, rats show novelty preference in all task variations. Impairments to WMC are seen under high-, but not low-, cognitive loads after high-THC smoke exposure, with no impact after high-CBD smoke exposure. This work introduces a novel behavioural task and scoring method, which evaluated WMC and may prove valuable across various behaviours and tasks.

P1-F-213: Nucleus accumbens glutamatergic afferents integrate outcomes in reward-learning

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The ability to integrate information about reward over time is essential to reward learning. While the role of dopaminergic inputs to the nucleus accumbens (NAc) is widely studied, the role of accumbens glutamatergic afferents in reward learning is relatively unexplored. Using in vivo fiber photometry, we simultaneously record population-level activity of medial prefrontal cortex (mPFC) and ventral hippocampus (vHIP) projections to NAc in male and female adult mice performing a two-armed bandit task. We find that both mPFC and vHIP projections to NAc dynamically encode information outcome history, with subtle sex- and pathway-way specific differences. mPFC-NAc tracks the recent history of reward and loss in females but only the recent history of loss in males. In contrast, vHIP-NAc preferentially encodes recent history of loss, but not reward. To determine the precise information encoded in these neural signals, we manipulated task design to systematically degrade behavioral requirements. This revealed that outcome history is tracked preferentially when linking a behavioral response with an outcome. However, when action-outcome pairing is not relevant, mPFC-NAc encodes immediate outcomes but not outcome history and vHIP-NAc fails to encode any outcome information. Together, these findings establish that mPFC-NAc and vHIP-NAc integrate outcomes over time when outcomes are contingent upon behavior and reveal a neural mechanism for the propagation of reward-associated information over time.

P1-F-214: Identifying neural circuit and molecular mechanisms underlying dopaminergic regulation of sleep in Drosophila melanogaster

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Sleep is an essential behaviour that restores energy and resources to maintain physical and mental health. In animals, dopamine signaling plays an important role in arousal by altering the activity of sleep-inducing neurons. In Drosophila, the dopamine receptor Dop1R2 has been shown to regulate sleep and is expressed in sleep regulatory circuits, but the mechanisms by which this Dop1R2 receptor regulates sleep are not fully understood. Accordingly, we confirm here that knocking down the Dop1R2 receptor

using RNAi across all neurons results in increased sleep, and we show similar results with multiple Dop1R2 mutants. To advance our understanding of Dop1R2 signaling, we have utilized TurboID proximity labeling proteomics and a neuronal RNAi screen to identify candidate Dop1R2 interactors that regulate sleep and arousal. Specifically, proximity labelling using an endogenously encoded Dop1R2-Turbo-V5 identified candidates with significantly increased abundance around Dop1R2 in in vivo environments. Interestingly, disruption of specific candidates pan-neuronally significantly alters day and night sleep. Further behavioral assays combined with live imaging will allow us to map the neural circuits wherein Dop1R2 and its interactors play a role in sleep and characterize how these interactions regulate Dop1R2 signaling and synaptic functions. This work will expand our understanding of how sleep is regulated at the molecular, circuit, and cellular levels, while providing a foundation to develop effective and targeted interventions for sleep disorders, such as insomnia and narcolepsy.

P1-F-215: A circuit-specific role for ifenprodil in blocking cocaine-induced habits

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Goal-directed decision-making - i.e., performing actions based on their expected outcomes - is a critically important behavioral adaptation. An over-reliance on inflexible habitual responding at the expense of goal-directed behavior represents a core feature of cocaine misuse. The orbitofrontal cortex (OFC) is essential for updating actions based on changes to contingencies. Cocaine use impairs goal-directed behavior and eliminates dendritic spines in the OFC; these effects are more pronounced in adolescents. We have previously shown that mice that are resilient against developing escalatory cocaine seeking display decreased expression of the GluN2B subunit of NMDA receptors in the OFC. Here, we show that ifenprodil, a GluN2B-selective antagonist preserves both goal-directed behavior and OFC dendritic spine densities in adolescent cocaine-exposed mice. Since ifenprodil prevents cocaine-induced loss of OFC dendritic spines, which are the principal post-synaptic sites of excitatory axonal projections, we hypothesized that dysregulation of inputs onto OFC neurons may be involved in the emergence of cocaine-induced habits. The OFC receives inputs from many brain regions, including major inputs from the basolateral amygdala (BLA), which plays a key role in memory consolidation. Here, we demonstrated that ifenprodil administration failed to protect against cocaine-induced habits when BLA to OFC connections were inhibited, suggesting that activity in this pathway is critical for typical adolescence associated OFC synapse maturation involving reduced GluN2B expression. These findings provide a deeper understanding of the effects of cocaine exposure in adolescence and could lead to future treatment options to prevent long-term decision-making impairments.

P1-F-216: Contingent and non-contingent punishment on oral morphine consumption in male and female rats

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Purpose: Altering opioid circuitry through uncontrollable stress could expose an overlap in analgesic and reinforcement systems. The present study investigates the effects of contingent and non-contingent punishment on oral morphine intake. Methods: Male and female rats were randomly assigned to one of five groups: Morphine Control (MC); Punishment (P); Yoked (Y); Shock Control (SC); and Chamber Control (CC). Following oral morphine acquisition, groups transitioned to the punishment phase. MC rats continued SA with no foot shocks (FS). P rats received FS at a 15% probability, contingent on active lever pressing for morphine. Y rats were matched with P to receive time-matched non-contingent FS during SA sessions. SC rats received matched FS, but never had access to morphine; CC rats never experienced FS or had access to morphine. Preliminary results: Male and female morphine controls are consuming similar amounts of drug in mg/kg. Contingent FS reduces drug intake in both, but the effect appears stronger in females. Non-contingent FS decreases consumption in males below baseline morphine control and this decrease is not observed in females. Implications: Fundamental research into how stressors interact with opioid reinforcement is important to further understanding of the role of these systems and how they help to integrate environmental exposures. Future research will compare baseline and post-training stress reactivity and pain responsivity via plasma corticosterone levels and tail-flick test, respectively, to determine shifts from the stressor and drug experience.

P1-F-217: Role of astrocytes in stress induced fear memory enhancement

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Stress has been shown to induce lasting memory alterations, with specific enhancement of emotional memory. Indeed, people that have previously experienced extreme adversity during childhood, i.e. early-life stress (ELS; e.g. neglect, abuse) have a higher incidence of psychiatric disorders. Many behavioural dysfunctions associated with ELS are faithfully reflected in rodent models, including enhancement of fear memories that are resistant to extinction. Preliminary data from our group suggest a strong role of glucocorticoid signalling in astrocytes in fear memory. Despite this, very little is known regarding the precise role of astrocytes in fear and emotionally salient memory. Here we set out to determine how astrocytes influence both the acquisition and extinction of fear memory. To do this we will use an auditory fear conditioning paradigm, followed by two days of extinction training. This behavioural paradigm will be combined with genetic targeting of astrocyte function using transgenic mice and viral approaches to determine whether, and how, astrocytes influence fear learning, memory, and extinction.

P1-F-218: Training of Morphine as an Interoceptive Negative-Feature Occasion Setter Alters Subsequent Morphine Reward

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Background: Feature positive (FP) and feature negative (FN) occasion setters disambiguate associations between exteroceptive conditioned stimuli (CS) and appetitive unconditioned stimuli (US). Training of

exteroceptive stimuli as occasion setters alters the incentive value of those stimuli, and incentive value is one characteristic of opioids that is related to their abuse potential. We investigated the effects of FP and FN training of an interoceptive morphine stimulus on subsequent morphine reward. Methods: Male and female rats were assigned to FP, FN, or control training groups. FP and FN rats received daily intermixed morphine or saline injections before training sessions. On morphine sessions, FP rats received white noise (WN) CS presentations that were followed by access to sucrose; sucrose was withheld on saline sessions. FN rats learned the reverse contingency. Controls received daily saline injections; sucrose was presented on half of sessions. Following training, rats entered place conditioning. Morphine was paired with a distinct context of a 2-sided chamber, saline with the other. During the preference test, rats had access to both sides of the chamber. Results: Male and female rats acquired the FP and FN discriminations. In males, morphine conditioned a place preference and this effect was not dependent on training history. Morphine also conditioned a place preference in FP and control females, but this effect was attenuated by FN training. Conclusion: Training experience with morphine as a FN occasion setter inhibits morphine reward in females. Attenuation of morphine reward by inhibitory training may be relevant to the treatment of opioid use disorder in women.

P1-F-219: Investigating the temporal dynamics of dichoptic masking

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In the standard model of binocular combination, inputs from the two eyes not only sum together but also suppress each other. Interocular suppression is often characterized through dichoptic masking, a phenomenon in which the detection of a target presented to one eye is reduced by a noise mask presented to the other eye. However, the temporal dynamics of interocular suppression are not well understood. In particular, the relationships between simultaneous masking, backward masking, and forward masking are not known for dichoptic stimuli. Our objective was to better understand these relationships. We employed a dichoptic suppression paradigm using a two-alternative-force-choice task. Stimuli were displayed on a passive 3D screen. Participants indicated the orientation of a target grating presented to one eye while a pink noise mask was presented to the other eye at the same spatial location but at a different time. The contrast of the target was adjusted using a 2-up 1-down staircase. Thirteen interstimulus intervals between the mask and the target were used to individually investigate the three masking types. Our results revealed the presence of a masking effect for all three masking types. Surprisingly, the strongest masking effect was found in the backward masking condition. These findings provide novel insight into the temporal dynamics of dichoptic masking, particularly in revealing the strong effect of backward masking, and may have implications in the general understanding of amblyopic suppression and in the development of suppression-related treatments for amblyopia.

P1-F-220: Sex and feature differences in the acquisition of Pavlovian cue-directed behaviour elicited by morphine

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Introduction: Morphine elicits interoceptive signals, which allow for the development of both appetitive (feature positive; FP) and inhibitory (feature negative; FN) Pavlovian drug-cue associations. There is evidence for sex and feature differences in the acquisition of both FN and FP associations; however, previous studies have used methodologies where associative learning is only assessed at the first of eight cue presentations within the session. Assessment of every CS-US pairing permits tracking learning patterns by sex and feature at every CS-US pairing. Methods: Male and female rats were assigned to FP or FN groups and received 96 intermixed morphine (3.2 mg/kg) or saline injections before a 4-min session with a single 15s white noise (WN) presentation. For FP rats, WN on morphine sessions indicated a 4s access to 0.1 mL of 26% sucrose solution and was withheld for FN. Saline indicated access for the FN rats and none for FP rats. Results: Females acquired FN and FP associations, and males acquired only FN associations. FN associations appear to be more easily acquired in both sexes. Conclusions: Typical Pavlovian drug discrimination uses multi-trial sessions, obfuscating assessment of trial-by-trial learning. Here we demonstrate that such learning can be investigated and potentially influenced by feature and sex.

P1-F-221: Effects of combined oral contraceptives on social recognition behavior in pubertal and adult mice

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Adolescence is a critical period of development during which several physiological and behavioral changes occur and are associated with fluctuating levels of endogenous sex hormones. In addition to endogenous sex hormones, many females are also exposed to different types of synthetic sex hormones as a hormonal contraceptive during adolescence. Yet, far too little is known about the nature of the effect they might induce on the brain and behavior. The aim of this study is to assess the effect of two types of combined oral contraceptives (COCs) on social recognition ability of pubertal and adult mice. A sample (n=70) of subjects were daily administered either an ethinyl estradiol/levonorgestrel (EE/LNG) COC, an ethinyl estradiol/drospirenone (EE/DRSP) COC or a vehicle at 5 or 10 weeks of age for 35 days. Social recognition task was conducted at week 7 of the experiment. Preliminary results indicate a sex difference in chemo-investigation time with males investigating more than females as well as a trend in mean difference between the EE/LNG treatment group and controls, with controls showing increased investigation time of the familiar stimulus mouse. This study will provide further understanding on the effects of COCs on cognitive functioning and women's health, which is fundamental as over 150 million women worldwide use COCs.

P1-F-222: Gaze patterns and brain activations in humans and marmosets in the Frith-Happé theory-of-mind animation task

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Theory of Mind (ToM) refers to the ability to attribute mental states to others. Research in humans has shown that mental state attribution can be evoked by animations of simple geometric shapes with different movement patterns (i.e., Frith-Happé animations developed by Abell et al., 2000). fMRI studies using Frith-Happé animations have revealed a distinct pattern of brain activations in frontal and temporoparietal regions during the observation of "ToM conditions" - showing two animated triangles moving in a way which indicates that one triangle reacts to the other object's mental state - compared to the "Random conditions" - showing the same two triangles moving and bouncing like objects. Currently, there is no evidence that nonhuman primates attribute mental states to moving abstract shapes. Here, we investigated whether highly social marmosets (Callithrix jacchus) process ToM and Random Frith-Happé animations differently. To directly compare humans and marmosets while viewing these animations, we used high-speed video eye tracking in twelve humans and twelve marmosets to measure saccades and fixations and we acquired ultra-high field fMRI data in ten humans at 7T and six marmosets at 9.4T. Our results show that both humans and marmosets 1) spent significantly more time looking at one triangle during the observation of ToM compared to Random animations, and 2) activated large and comparable brain networks when viewing ToM compared to Random animations, with activations in brain areas previously associated with ToM processing in human subjects. The results indicate that marmosets, similar to humans, process ToM and Random animations differently. This opens the possibility that marmosets, like humans, may be able to attribute mental states to these animations.

P1-F-223: Lateral hypothalamus-dorsal raphe nucleus circuitry: anatomy and function in emotional behaviors

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The dorsal raphe nucleus (DRN) regulates affective behaviors and energy balance. Emotional states might be encoded in DRN by neural inputs from numerous brain regions. Although one of the major reciprocal synaptic partners of DRN is the lateral hypothalamic area (LHA), the circuitry between LHA and DRN was not characterized yet. In the current study, we use anterograde and retrograde viral strategies to investigate the anatomical and functional reciprocal circuitry between the LHA and the DRN. Specifically, we targeted DRN cells receiving input from LHA (DRN input) and DRN cells projecting on LHA (DRN output) to express either fluorescent proteins or genetically-encoded calcium indicators. Our results show that DRN input and DRN output neurons are largely two distinct neuronal populations that have differential spatial distribution. LHA makes synaptic contact with 5-HT and non-5-HT neurons in the DRN, which is spatially biased to the ventromedial part and dorsolateral parts of the DRN, respectively. DRN output neurons appeared to be mostly non-serotonergic indicating the bias of the retroAAV-FlpO used. Both DRN input and DRN output neurons target a stereotypical set of subcortical regions while there were no terminals detected in cortical areas. Neural activity of studied populations was increased in aversive stressful contexts such as air puff and tail suspension. Overall, these results show that 1) anterograde transsynaptic tracing can be applied to identify DRN neurons innervated by the LHA, 2) LHA targets specific DRN neuron populations with a spatial bias, 3) DRN input neurons projects mostly to subcortical limbic regions 4) DRN input and DRN output neurons are involved in encoding aversive signals.

P1-F-225: Nicotine and cigarette smoke extract are not discriminated in an appetitive pavlovian task in male and female 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 ~8000 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. Significance: This has important implications for ongoing discussions regarding the validity of nicotine as a proxy for tobacco in animal models.

P1-F-226: Functional parcellation of the common marmoset's cerebral cortex with movie-driven ultra-high field fMRI

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The primate brain is composed of a dense mosaic of brain areas often distinguished according to their function, cytoarchitectonic structure, or connectivity. Outlining its functional organization is therefore a fundamental step in understanding how and where information is processed at the cortical level. To characterize the common marmoset's (Callithrix jacchus) functional cortical architecture, we took advantage of ultra-high field (9.4T) functional MRI data from 9 awake marmosets during the presentation of a 33-minutes naturalistic movie containing a wide variety of visual and acoustic stimuli. Using a data-driven hierarchical clustering approach, we isolated several functional networks related to the processing of different sensory information and/or to different cognitive processes. Clustering is achieved by averaging the 1325 time-points that compose the average time-courses of an entire scan session for each gray matter voxel. From these average time-courses, we computed a 2D correlation matrix between the time-course of all the cortical voxels. By measuring the standard Euclidean distance between each pair of correlation values, we created the hierarchical cluster tree using Ward's method for linkage. Among the clusters thus defined, some overlap with sensory areas previously described, such as the primary auditory cortex or different portions of the visual cortex; others include areas involved in specific functional processes (as for the face/body-parts network or three distinct somato-motor networks). The functional parcellation presented here therefore provides a solid basis for the localization of cortical areas characterized by different functional features, acting as a possible localizer for future studies in multiple sensory and cognitive domains.

P1-F-227: Are crossed and uncrossed disparities processed by the same mechanism?

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Stereopsis allows us to judge if objects are in depth and whether they lie "in front of" (crossed disparity) or "behind" (uncrossed disparity) the fixation plane. However, it remains unclear whether this ability to judge depth polarity relies on a single mechanism or whether there are separate mechanisms encoding crossed and uncrossed disparities. In this study, a "2-by-2 forced-choice paradigm" was used. This paradigm involved two intervals of presentations: a target stimulus and a null stimulus. Subjects were asked to respond not only in which interval the stimulus appeared, but also judge which of two possible stimuli (crossed or uncrossed) it was. The first decision provided information about detection while the

second one provided information about discrimination. If discrimination can be achieved at the detection threshold, we would conclude that there are separate cross and uncrossed disparity channels. Surprisingly a degree of inconsistency was discovered among people: some subjects showed strong bias towards crossed or uncrossed disparity; some didn't reach 100% identification performance even at large disparities. Additionally, some performed better in discrimination than in detection. These results suggest that there is no stable and consistent relation between when the depth of a stimulus can be detected and when its depth polarity is known. Either this is an inherent instability in the stereoscopic system across individuals or it reflects a measurement instability within any one individual. Our next step is to resolve which of these two conclusions is correct.

P1-F-228: Voluntary direction of attention affects physiological responses to sounds in misophonia

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In the presence of specific trigger sounds, people with misophonia demonstrate exaggerated emotional responses and heightened autonomic arousal. Although recent findings have highlighted the importance of higher-level cognitive processes in misophonia, we have little insight into how these processes could be used to modulate misophonic responses. Because individuals with misophonia often report attending to music to divert their attention from triggers, we explored how physiological responses in misophonia could be modulated by attending to dichotically-presented musical excerpts, or trigger sounds. Participants with misophonia and healthy controls completed a task in which they were presented with music (unfamiliar piano pieces) in one ear while neutral sounds, generally unpleasant sounds, or typical trigger sounds played in the other ear. During each trial, a visual prompt indicated which ear (left or right) participants should attend to. Measure of physiological arousal (i.e., pupil dilation, heart rate variability, skin conductance responses) were continuously recorded throughout the experiment. We report differences in physiological responses in people with and without misophonia, as they selectively attend to trigger and control sounds presented simultaneously and separately. Our study represents a first investigation of the effectiveness of voluntary attentional modulation on misophonic reactions. We aim to increase our insight into how high-level processes are involved in misophonia, and how they can be used to modulate problematic reactions.

P1-F-229: Non-visual summary statistics can be extracted from visual scene ensembles

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Past literature has suggested that summary statistics for groups (i.e., ensembles) of faces or objects can be rapidly extracted. Recently, Tharmaratnam and colleagues (VSS 2019) demonstrated that the average scene content (i.e., perceived naturalness or manufacturedness) and spatial boundary (i.e., perceived openness or closedness) of scene ensembles can be extracted, without reliance on visual working memory (VWM). Moving beyond visual scene features, Jung and Walther (2021) have shown that complex non-visual attributes (i.e., apparent sound level: how quiet or loud a scene would sound; and

apparent temperature: how hot or cold a scene would feel) of single scenes are represented in the prefrontal cortex and are accurately rated by observers. Here we examine if these complex non-visual attributes can be extracted from scene ensembles, with or without VWM. Participants rated the average apparent sound level (Exp. 1) or temperature (Exp. 2) of scene ensembles. In both experiments, we varied set size by randomly presenting 1, 2, 4, or 6 scenes to participants on each trial, and measured VWM capacity using a 2-AFC task. We found that participants were able to accurately extract summary statistics for both ensemble scene features, with all 6 scenes being integrated into their percepts. This occurred without relying on VWM, as less than 1.3 scenes were remembered on average. Overall, these results reveal the flexibility of ensemble coding to encode multisensory features, to efficiently capture environmental fluctuations.

P1-F-230: Comparison of Male and Female Avoidance, Darting, And Freezing Behavior Within the SPS Model

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Post-traumatic stress disorder (PTSD) is more likely to develop in women compared to men after trauma exposure. The sex differences in symptom manifestation are not well understood. The goal of this study was to use the single prolonged stress (SPS) rodent paradigm of traumatic stress to identify the different persistent fear-like behavioral symptoms male vs. female rats manifest after exposure to a traumatic experience. In experiment 1 we used a cued escape paradigm to examine the effects of SPS on acquisition and extinction of freezing and escape induced by a CS tone. In experiment 2 we used the inhibitory/passive avoidance paradigm to examine the effects of SPS on acquisition and extinction of freezing and avoidance induced by an aversive context. In experiment 1, the behavior observed in this paradigm did not allow for comprehensive experiments and the results were inconclusive. The results of experiment 2 suggested that when males can avoid an aversive context, SPS deficits in the retention of extinction are not observed. Avoidance and freezing during extinction testing were negatively correlated with high levels of avoidance being associated with low levels of freezing in control female rats. SPS/female rats exhibited higher avoidance with no concomitant decrease in freezing during extinction testing. These findings suggest that males and females respond differently to traumatic stress. The results of this research further emphasize the need for determining if trauma leads to persistent fear via different circuits and behavioral mechanisms in males vs. females.

P1-F-231: Mice can monitor their temporal judgment errors

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The ability to accurately monitor the passage of time is pivotal for many functions such as associative learning and planning. Our earlier experiments show that humans and other animals can integrate their representational uncertainty about time intervals into decisions in a nearly normative fashion,

suggesting that they can monitor their timing errors. This can be formalized as knowing whether and how much they have under- or overestimated the duration of an event without any feedback, which we refer to as metric error monitoring (MEM). Although MEM has been documented in humans and recently in rats (with two choice procedure), whether mice can monitor their timing errors based on confidence-like measures is unknown. We tested this hypothesis in 18 C57BL/6 male mice. Mice were trained to depress a lever at least for a target duration in order to receive a reward in the food hopper. No reward was given in trials where mice under-produced the target. During test trials, the rate of nose-pokes into the food hopper during a variable response window after pressing the lever was recorded. Higher rates of nose-poking in trials with temporal productions at or above the target duration compared to short temporal productions demonstrate that mice could better than chance judge whether or not their temporal production was close to meeting the task criterion to receive a reward. These results suggest temporal error monitoring abilities in mice and provide the necessary behavioural means to study its neural basis based on correlational and manipulative methods in non-human animals.

P1-F-232: Identifying neocortex L6b neuronal diversity and subpopulations in the mouse and human brain

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Understanding the diversity of neuronal subpopulations is crucial to elucidating the brain's cellular composition and function. To investigate whether neuronal properties of Layer 6b (L6b) of neocortex are heterogenous, we performed a multidisciplinary investigation in the mouse and human brain. To establish whether subpopulations exist within L6b we analyzed single-cell RNA sequencing (scRNA-seq) data from mouse primary motor area and human medial temporal gyrus. Using dimensionality reduction techniques, we found that L6b excitatory neurons formed 4 transcriptomically distinct subpopulations in the mouse brain, expressing unique receptors such as the hypocretin/orexin receptor 2 (Hcrtr2) and the serotonin receptor 1D (Htr1d), and 3 transcriptomically distinct subpopulations in the human brain, similarly expressing unique receptors as Hcrtr2. We subsequently validated these subpopulations with immunohistochemistry. We then sought to understand if L6b neurons may have subtype-specific electrophysiological or connectivity properties. We found that L6b neurons are more excitable, have a higher firing threshold, faster recovery times, and lower after-hyperpolarization potentials relative to Layer 6 neurons. Additionally, a specialized population of L6b neurons ramifies in Layer 1 of neocortex. These findings support that L6b neurons entail a level of heterogeneity spanning multiple domains: transcriptomic, electrophysiological, and connectivity properties. In the future, these results can be used to understand functional cell-type-specific differences within neocortex L6b.

P1-F-233: Respiration organizes gamma synchrony in the prefronto-thalamic network

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Multiple cognitive operations are associated with the emergence of gamma oscillations in the medial prefrontal cortex (mPFC) although little is known about the mechanisms that control this rhythm. Using local field potential (LFP) recordings from cats, we show that periodic bursts of gamma recur with 1 Hz regularity in the wake mPFC and are locked to the exhalation phase of the respiratory cycle. Respiration organizes long-range coherence in the gamma band between the mPFC and the nucleus reuniens the thalamus (Reu), linking the prefrontal cortex and the hippocampus. In vivo intracellular recordings of the mouse thalamus reveal that respiration timing is propagated by synaptic activity in Reu and likely underlies the emergence of gamma bursts in the prefrontal cortex. Our findings highlight breathing as an important substrate for long-range neuronal synchronization across the prefrontal circuit, a key network for cognitive operations.

P1-F-234: Depth-cue invariance of unfamiliar objects: a psychophysics study

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Entire object categories and complex objects such as faces are recognized independently of depth-cue 1,2, implying the visual system must support depth-cue invariance, in the same way that it supports size and position invariances 3,4. However, we know that faces are processed differently -'faces are special'--, as suggested by holistic theories and studies that show for e.g., part-whole effects 5, inversion effects 6, composite effects 7. Since our visual cortex is not naturally tuned to unfamiliar stimuli, if depth-cue invariance is indeed a general property of object recognition, it should be present for unfamiliar object identities. We tested the hypothesis that the perceptual representation of unfamiliar object identities is equivalent regardless of depth-cue. 70 participants with normal or corrected-to-normal vision performed the psychophysics task online. Stimuli were 11 coin-shaped abstract objects, rendered using either shading, structure-from-motion or texture depth-cues. Objects of a single depth-cue were randomly displayed, and rated from 1--not similar at all to 5--extremely similar for all object pairs. Perceptual representation of objects was measured using the representational similarity structure, namely by constructing representational similarity matrices generated by averaging pairwise similarity ratings of objects. Statistical analyses were performed by permuting the representational matrices. Correlations between all three depth-cue similarity matrices were statistically significant when compared to permuted data (all rho >= .6 ± .29, p <.01, Bonferroni corrected). The similarity structure of unfamiliar objects is behaviorally comparable between depth-cues, supporting the depth-cue invariance hypothesis as a general property of object recognition.

P1-F-235: Voluntary direction of attention affects physiological responses to sounds in misophonia

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In the presence of specific trigger sounds, people with misophonia demonstrate exaggerated emotional responses and heightened autonomic arousal. Although recent findings have highlighted the importance of higher-level cognitive processes in misophonia, we have little insight into how these processes could

be used to modulate misophonic responses. Because individuals with misophonia often report attending to music to divert their attention from triggers, we explored how physiological responses in misophonia could be modulated by attending to dichotically-presented musical excerpts, or trigger sounds. Participants with misophonia and healthy controls completed a task in which they were presented with music (unfamiliar piano pieces) in one ear while neutral sounds, generally unpleasant sounds, or typical trigger sounds played in the other ear. During each trial, a visual prompt indicated which ear (left or right) participants should attend to. Measure of physiological arousal (i.e., pupil dilation, heart rate variability, skin conductance responses) were continuously recorded throughout the experiment. We report differences in physiological responses in people with and without misophonia, as they selectively attend to trigger and control sounds presented simultaneously and separately. Our study represents a first investigation of the effectiveness of voluntary attentional modulation on misophonic reactions. We aim to increase our insight into how high-level processes are involved in misophonia, and how they can be used to modulate problematic reactions.

P1-F-236: The effects of daily variability in sleep quality on cognitive fluctuations in older adults

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Over half of older adults report occasionally or regularly having difficulty falling asleep or staying asleep. Insufficient sleep quality and quantity can occur because of age-related changes in the central nervous system, or due to other physiological conditions that result in interrupted sleep and nocturnal awakenings. Sleep problems have been associated with poorer indices of cognitive function such as processing speed, memory, and inhibition, and are associated with an increased risk of developing neurocognitive disorders. Most studies on sleep quality and cognition have been cross-sectional, and it is unclear how daily fluctuations in sleep quality affect cognition. The aim of the current project is to characterize the association between sleep quality and day-to-day fluctuations in the cognitive performance of older adults. We report results from a pilot sample of older adults (N=10) who wore an electroencephalography (EEG) headband for 14 nights. After awakening and achieving alertness, participants fill out a daily sleep log and completed computerized cognitive tasks which yield measures of reaction time, inhibition, cognitive flexibility, and sustained attention. We correlate daily changes in these measures with neurophysiological measures of sleep quality (i.e., frequency and duration of wake after sleep onset (WASO) per night; NREM and REM sleep duration). We also report on the feasibility of multi-day in-home recordings using EEG and cognitive tasks, with a view to larger studies and finer characterization of sleep-performance relationships in older adults.

P1-F-237: Comparing theta band activity of rapid-eye movement (REM) sleep and working memory using MEG

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Working memory is a cognitive process in which items are held in mind so that they can be mentally manipulated. It is tightly tied to neural oscillations in the theta band (4-8 Hz), which appears over medial frontal and dorsal parietal regions during tasks that require manipulation in memory. Interestingly, theta-band activity is also a prominent feature of rapid eye-movement (REM) sleep. Theta-band activity in REM has been causally implicated in hippocampus-dependent memory consolidation. However, little is known about the function of cortical theta oscillations recorded in EEG in REM. To explore the similarities between working memory and REM theta, we recorded electroencephalogrpahy (EEG) and magnetoencephalography (MEG) overnight in 10 healthy young adults and identified 5s windows of REM sleep into phasic (dense eye movements) and tonic (low eye movement) periods. We also recorded similar data in 17 healthy young adults as they performed an auditory working memory task and identified time periods in which participants were manipulating tone patterns in mind. In both cases, we analyze oscillatory power in the theta band and map it to subject-specific brain anatomy using distributed source models. We also conduct connectivity metrics to quantify inter-region communication within the theta band and report similarities and differences in brain activity. Comparing brain activity associated with working memory and activity in the same frequency band in REM sleep may be a first step towards better understanding REM sleep's cognitive functions.

P1-G-238: The correlations between the volumes of cerebellar transverse zones and lobules in relation to healthy individuals' age and sex

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Background: Brain atrophy is one of the critical features of aging, and cerebellar atrophy is not an exception. It is well known that the cerebellar cortex is organized in transverse zones and lobules; each plays different roles ranging from motor to cognitive functions. The volume changes of different cerebellar zones and lobules are still poorly understood and need to be addressed considering both females and males. Methods: To determine the effects of sex and age on the volume of cerebellar transverse zones and lobules in healthy people, we have investigated the correlations between cerebellar volumes and age in the cerebellum of 876 healthy individuals (age range: 18-94, 58.1% female) whose MRI scans were drawn from the IXI and OASIS database. Results: Tests of between-subjects effects revealed a negative linear relationship between cerebellar regional volumes and age in both females and males. In addition, adjusted total cerebellum and different transverse zones are significantly high in healthy females than those in males. Also, over age, there is a significant drop in cerebellar volume in both sexes, and the reduction is significantly sharper in men. Conclusion: These findings might help create a standard pattern for human cerebellar volume changes in the subsets of transverse zones and lobules that will help address pathological age-related cerebellar disorders.
Keywords: cerebellum, aging, cerebellar volume changes, cerebellar zones, cerebellar lobules, sex difference

P1-G-239: Accelerated transcranial ultrasound neuromodulation in Parkinson's Disease: a pilot study

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Introduction: Non-invasive brain stimulation (NIBS) is a promising clinical tool for the treatment of motor symptoms in Parkinson's Disease (PD). We investigated the effects of accelerated theta burst TUS (a-tbTUS) on clinical MDS-UPDRS III outcomes and TMS measurements in PD patients. Methods: Each patient participated in two study visits, with either active or sham TUS in random order. a-tbTUS was administered to bilateral M1 in 3 sessions (80 s sonication time for each session) at 30 minute intervals. All patients were tested OFF medication. Transcranial magnetic stimulation (TMS)-elicited motor-evoked potentials (MEP) as measure of motor cortex excitability were taken at each visit. Clinical outcomes were assessed using the motor Unified Parkinson's Disease Rating Scale (UPDRS-III) and were video recorded. Statistical analyses were performed on outcome measures and paired t-tests were used to determine significance. Results: A total of 20 visits were completed in 10 PD patients. MEP amplitude significantly increased following active sonication, but not sham sonication compared to baseline ($p = 0.0057$). MEP amplitudes were significantly higher ($p=0.0064$) following active a-tbTUS compared to sham stimulation. There were no statistically significant differences in global UPDRS-III scores between the two groups, although qualitative improvement in upper extremity rigidity was noted in 50% of patients in the active condition, relative to 30% of patients in the sham condition. Conclusion: This is the first study to assess the impact of an accelerated tbTUS protocol in PD. Our findings demonstrate that a-tbTUS is a feasible non-invasive neuromodulation strategy in PD and may impact motor cortex excitability.

P1-G-240: Rapid, high-efficiency differentiation of motor neurons from human pluripotent stem cells

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Human motor neuron (MN) diseases include devastating disorders such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA). A reliable human MN model is critical to uncover disease mechanisms. Here we present the STEMdiffTM Motor Neuron Culture System which generates MNs from human pluripotent stem cells (hPSCs) at high efficiency. The hPSCs were aggregated to embryoid bodies (EBs) with STEMdiffTM Motor Neuron Differentiation Kit in an ultra-low attachment or an AggreWellTM400 plate. On day 9, EBs were dissociated into single cells and replated for adherent culture. On day 14, the cells were either matured using the STEMdiffTM Motor Neuron Maturation Kit or assessed by immunocytochemistry and qPCR for motor neuron markers BIIITUB, ISL1, and HB9. The MNs were co-cultured with either myotubes generated using MyoCultTM Differentiation Kit (Human) or with microglia generated using STEMdiffTM Microglia Kits for one week, and then analyzed via immunocytochemistry. A highly pure population of MNs was observed at day 14 (BIIITUB: 92.6 ± 3.7%; ISL1: 56.0 ± 13.9%; HB9: 65.2 ± 13.2%; mean ± standard deviation, n = 6) with cervical identity by the expression of HOXA5 through qPCR. After two weeks in the maturation medium, the MNs showed high expression of mature markers including CHAT, MAP2 and SYP. Finally, MNs were successfully co-cultured with hPSC-derived myotubes or microglia for one week. Taken together, STEMdiffTM Motor Neuron

Culture System provides a powerful tool to generate hPSC-derived MNs and co-culture systems for in vitro studies of human MN diseases.

P1-G-241: Development of a complex geometry small-caliber tissue-engineered blood vessel model for the study of intracranial aneurysms

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Intracranial aneurysms (IA) are a weakness of the artery wall causing ballooning that mostly occurs in the circle of Willis junctions. The risk of rupture and the following subarachnoid hemorrhage, which have devastating consequences for patients, are difficult to evaluate and require specialized imaging. The objective of this study is to develop a complex junction geometry small-caliber tissue-engineered blood vessel (TEBV) model for the study of IAs. An innovating spherical seeding system to produce complex TEBV models was developed. Polyethylene terephthalate glycol (PETG) scaffolds of a "Y" geometry and human vascular cells are placed inside customized seeding chambers for uniform cell distribution. The seeded PETG scaffolds are cultured for 21 days before this first layer of reconstructed tubular tissue is seeded again and matured another 21 days. Histological cross-sections were taken to measure tissue thickness. Cell viability was evaluated by flow cytometry. An innovative spherical seeding system will be presented with optimized parameters. TEBV after 42 days of culture have uniform tissue thickness at the branches and junction of the "Y". Cell viability after seeding with this system is superior to other methods shown. This novel 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-242: On the shape of representational geometry

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Representational similarity analysis (RSA) is a powerful tool for interrogating brain function by studying the geometry of neural representations of stimuli. However, typical RSA analyses use linear methods, and we argue that linear methods can not capture essential non-linear aspects of representational geometry. By leveraging the power of topology, a mathematical tool for studying certain non-linear shape objects via distances between their points, we augment RSA to be able to detect more subtle, yet real, differences and similarities in representational geometry, and to be able to compare RSA data across studies. This new method could be used in conjunction with regular RSA in order to study non-linear brain function and discover new and exciting inferences about how the brain works with high levels of statistical power.

P1-G-243: The matrisome formed by skin fibroblast cultured in 3D promotes neurogenesis in silico

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Neurogenesis in an adult human brain remains a debatable area of research, but clear evidence has shown that components of the matrisome partly orchestrate the formation of new neurons. The matrisome is defined by the ensemble of genes encoding extracellular matrix (ECM) proteins. ECM-associated proteins are known to have essential functional roles during the development, plasticity and regeneration of the CNS. It has been shown that tissue-engineered skin model, made of patient's dermal fibroblast, recapitulated some specific neuropathological features of ALS and NF1. In-depth analysis of the tissue-engineered skin's matrisome would be of particular interest in the field to further confirm the usefulness of such in vitro model for the study of neurological diseases. Dermal fibroblasts were cultured in monolayer or three-dimension (3D) using the self-assembly approach. Total proteins were identified and quantified by LC-MS/MS. The MatrisomeDB 2.0 database was then used to categorize matrisomal proteins. Modulated proteins in the self-assembled dermis were analyzed in silico. Self-assembled dermis comprised 3049 proteins and 129 were listed as a part of the matrisome. Meanwhile, 71 and 20 matrisomal proteins were significantly up- and down-regulated, respectively. Quite interestingly, in silico analysis using the generated proteomic data, revealed that neurogenesis was predicted to be strongly stimulated in such tissue-engineered model. 3D skin fibroblasts express specific ECM proteins that could activate neurogenesis. Patient-derived dermal fibroblasts, cultivated in 3D, could therefore be useful for the study of neurological diseases and be a less invasive approach than brain biopsies, to model complex neurological disorders in vitro.

P1-G-244: Building a better psychedelic

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For millennia, humans have consumed psychedelic drugs for spiritual and therapeutic benefit; still, the neurological mechanisms underlying their profound effects are largely unknown. Classical tryptamine-based psychedelics, including psilocybin and di-methyl tryptamine (DMT), closely resemble serotonin, a neurotransmitter essential for mood regulation, and were thought to primarily work via serotonin receptors, particularly 5-HT2A receptors (5HT2AR). 5HT2ARs play a noteworthy role in moderating emotional output and are a popular pharmacological target in the treatment of depression and anxiety, though the majority of these treatments have problematic side effects and low efficiency. Additionally, 5HT2ARs also mediate the head twitch response (HTR) which is commonly used as a hallucinogenic proxy in rodents. Importantly, this project is sponsored by Enveric Bioscience Inc, a Calgary-based bio-technology company, which aims to elucidate how the chemical features of a psychedelic drug relate to its hallucinogenic and stress-altering capacity. Here, in collaboration with the CSM Optogenetics Core Facility, we have developed a machine-learning based annotation tool for automated analysis of HTR, as

well as a variety of other behavioural readouts. The goal of this project is to investigate the hallucinogenic capacity and stress-reducing ability of various psychedelic drugs and ultimately provide relief for individuals suffering from stress-related disorders.

P1-G-245: Differential effects of inflammatory molecules on ionized calcium-binding adapter molecule 1 (IBA1) expression in brain organoids with innate, proteostatic microglia

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Microglia are the innate immune cells of the brain, and help maintain homeostasis and regulate synaptic development as well as facilitate the maturation of other brain cell types. Historical approaches to the study of functions of microglia have significant disadvantages. For example, microglia in monoculture have abnormally high levels of 'ionized calcium-binding adapter molecule 1' (IBA1), indicating immune activation and a non-physiological phenotype. Interspecies differences further complicate any translation of observations to the human context. Three-dimensional cultures such as brain organoids may help overcome these limitations. Brain organoids are an aggregate of different brain cell types that exhibit relevant cytoarchitectural layering. Current protocols generate brain organoids 1) devoid of microglia, or with 2) immunocompromised or 3) genetically modified microglia. We developed a new protocol to generate human brain organoids with innate, immune responsive microglia without the need for genetic modifications. Importantly, these organoids express low basal levels of IBA1 and thus display a protein signature of homeostatic microglia. We tested 19 inflammatory molecules on male and female organoids, and demonstrate increased IBA1 expression in response to a subset of these molecules, indicating a normal microglial immune response. Our brain organoids provide a platform to study functions and responses of human microglia in an environment that is easily manipulatable and, importantly, more relevant to the human context.

P1-G-247: Label-free neural cell phenotyping by measuring various biophysical properties with quantitative-phase digital holographic microscopy

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Progress achieved in the field of stem-cell technology allows the reprogramming of patient-derived cells, obtained from urine samples or skin biopsies, into so-called induced pluripotent stem cells (iPSCs) that can then be differentiated into any cell types, including neural cells. Within this framework, techniques, being able to accurately and non-invasively characterize cell structure, morphology, and dynamics, represent very promising approaches to identify disease-specific cell phenotypes. With this objective in mind, we will present how quantitative-phase digital holographic microscopy (QP-DHM) along with various experimental developments to analyze its quantitative-phase signal (QPS) constitute a very appealing live-cell imaging technique to identify specific neural cell phenotypes. To this end, we have

developed several methodologies and paradigms, involving fluidic devices, micro-structured coverslips, as well as perfusions of physiological media with refractive index gradients, to accurately measure a wide range of neural cell biophysical properties including, among others, the intracellular refractive index, the cellular dry mass, the cell height, the cell membrane fluctuations, and the absolute cell volume. In conclusion, QP-DHM provides an innovative approach for identifying disease-specific cell phenotypes in neurosciences thanks to its capacity to quantitatively measure in a non-invasive manner a wide variety of neural cell biophysical properties from the QPS through different experimental methodologies and paradigms involving, in particular, microfluidics.

P1-G-248: Combining NGN2 programming and dopaminergic patterning for a rapid and efficient generation of hiPSC-derived midbrain neurons

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Parkinson's disease (PD), the most common movement disorder, is characterized by the massive and progressive loss of dopaminergic (DA) neurons from the substantia nigra pars compacta. The exact mechanisms behind PD pathogenesis and the vulnerability of the DA neuronal population are not fully elucidated. The use of human derived induced pluripotent stem cells (hiPSCs) differentiated to DA neurons offers a valuable model to decorticate the cellular and molecular mechanisms PD pathogenesis. Recently, the description of a new approach of induced neuronal cell differentiation through the programming by the transcription factor NGN2 has shown to efficiently induce rapid differentiation of multipopulational neurons. We combined NGN2 programing and the use of commercially available midbrain differentiation kits to force iNeurons differentiation into mature and functional DA (iDA) neurons. We used immunocytochemistry, gene expression analysis, and functional characterization to confirm the identity and the functional characteristics of iDA neurons. Finally, we investigated the utility of our approach by assessing iDA selective vulnerability to the neurotoxin 6-OHDA. Our study shows that by using NGN2 derived neurons combined with the use of commercially available midbrain defined media allows for the generation of a high (60%) homogenous population of midbrain DA neurons in a short lapse of time. These iDA neurons exhibit midbrain neuronal characteristics, can produce and release DA and are electrically and synaptically active as early as DIV 18. In conclusion, our work introduces a highly robust optimized protocol for DA neuron differentiation from hiPSCs, which we believe has potential capabilities for studying the pathogenesis of PD.

P1-G-249: The difference in poststimulus suppression between residual inhibition and forward masking

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The phenomenon of tinnitus masking (TM) and residual inhibition (RI) of tinnitus are two ways to investigate how external sounds interact with tinnitus: TM provides insight on the fusion between external sound activity and tinnitus related activity while RI provides insight on how the external sound might suppress the tinnitus related activity for a period of time. Differences in masking level between the tinnitus and an external tone with tinnitus characteristics (frequency, loudness) have previously shown a high level of heterogeneity. The difference in poststimulus suppression between residual inhibition and forward masking has never been explored. This study aims to investigate minimum masking levels (MMLs) and minimum residual inhibition levels (MRILs) of tinnitus and of an external tone mimicking tinnitus. Pulsed narrowband noises (1 octave width and centered at 1 kHz, frequency of the hearing loss slope, tinnitus frequency) and white noise were randomly presented to 20 tinnitus participants and 20 controls with an external tone mimicking tinnitus (4 kHz, intensity level corresponding to tinnitus loudness). The MML values obtained for the masking of tinnitus and for the mimicking external sounds were very similar. On the other hand, the MRILs were significantly different between the tinnitus and the mimicking external sounds within tinnitus participants. They were also different between the tinnitus participants and the controls. Overall, for both within and between comparisons, the MRIL values were much higher to produce a poststimulus suppression for the mimicking sound than for the tinnitus. These results corroborate other findings suggesting that the tinnitus-related neural activity is very different from the stimulus-related neural activity.

P1-G-250: Gel nail polish as an alternative to traditional coverslip sealants: a quick solution to a sticky situation

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A widespread standard protocol to seal coverslips on a microscope slide for histological analysis utilizes air-drying nail polish. With this method, nail polish is applied to glue the coverslip in place and prevent the leakage of mounting media. Following its application, the sealed slide is then left to air-dry prior to imaging. Drying takes time, typically overnight, and generates an unpleasant smell. Equally familiar is the waiting game that comes with the drying period, lightly touching the polish to check its dryness, while being careful not to disrupt the coverslipped sample, often leaving spots of sticky polish on one's fingertips. An advantageous solution to these drawbacks is to use gel nail polish, which rapidly hardens and dries by being cured under a UV lamp. Here we show that UV-cured gel polish can effectively replace air drying nail polish. Gel nail polish presents a rapid, scentless, non-toxic, and cost-effective solution to coverslip sealing. Cured in 10 seconds, with no impact on fluorescent labels, the gel polish hardens rapidly and the slide is immediately ready to be imaged. Furthermore, we show that gel nail polish can be used to rapidly generate 3D ridges and structures to support coverslipping and imaging of thicker tissue sections and samples. Gel nail polish is purposefully unscented, and the brands used in our study employ environmentally conscious, vegan, and cruelty-free ingredients. UV-cured gel nail polish is a cost-effective alternative that presents an easy, accessible, and inexpensive solution to traditional coverslip sealing methods.

P1-G-251: Biophysical simulations of aperiodic scalp potentials establish a physiologically grounded method for detrending EEG spectra

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Electroencephalograms (EEGs) display a mixture of periodic and aperiodic fluctuations. Almost a century of research has established that periodic EEG signals are generated by synchronous neural oscillations. In contrast, aperiodic EEG signals remain poorly understood. Whereas periodic EEG signals produce peaks in power spectra, the aperiodic component manifests as a background spectral trend that decays with apparent 1/fβ behaviour. Differences in the spectral exponent, β, have been correlated with aging, cognitive performance, neurological disorders, anesthesia, and sleep. In addition to being a useful biomarker, it has been suggested the 1/f trend in EEG spectra should be removed prior to quantifying neural rhythms. Although increasingly popular, removing the 1/f component from brain rhythms continues to lack a clear theoretical motivation and interpreting 1/f differences remains speculative. Using biophysically detailed simulations, we investigated scalp potentials generated by neural networks with a range of dynamic behaviours. We show that the aperiodic component of EEG spectra reflects a combination of functional synapse clustering, network correlation timescales, and GABA receptor kinetics. Our model explains that past methods for quantifying periodic EEG can be confounded by changes to synaptic physiology, but not by other factors. Consequently, normalizing spectra to baseline or the fitted 1/f component can both yield incorrect conclusions. Overall, our work develops a biophysically grounded theory describing the neural basis of aperiodic scalp potentials and provides practical conclusions for the spectral analysis of EEG data.

P1-G-252: Robustness of differential neurophysiological effects between parkinson's disease and healthy control groups

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Differential effects in non-invasive magnetoencephalographic (MEG) recordings between clinical and healthy cohorts hold promise as biomarkers of neurological conditions. However, the robustness of these between-group effects against the variable duration of patient recordings needs to be established to ensure they are clinically valid. We examined the minimum recording duration required to obtain robust group differences in the frequency spectrum of resting-state brain activity between patients of Parkinson's disease (PD) and age-matched healthy controls (HC). We define the time-to-stability indicator (T2S) as the minimal length of data required beyond which less than 1% change is observed in between-group estimates. By simulating realistic MEG time series to instantiate varying sample and effect sizes, we estimated the T2S of four disease-relevant group-wise spectral contrasts. We found that the robust detection of shifts in alpha peak frequency required at least 480s consecutive data length, 240s for differences in peak amplitude at alpha and beta frequencies, and 300s for detectable differences in aperiodic exponents. Then, by using empirical MEG recordings from PD (N=79) and HC (N=54), we verified that between-group differences in frequency peak amplitude required about 240s to

enable robust detection, and peak shifts did not stabilize within 390s of the available recordings. In sum, we propose a novel framework for testing the robustness of clinical neurophysiological effects by leveraging both simulated and empirical MEG data. We anticipate this approach will help define guidelines for other clinical research designs using similar data modalities such as EEG.

P1-H-253: The Financial Needs and Requests of Brain Tumour Patients in Ontario through GoFundMe

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Brain tumour patients across Ontario experience the financial stress of paying for treatments such as chemotherapy. However, in addition to medication, there are numerous other financial burdens placed on patients such as costs of transportation, loss of income, time off work, mobility equipment, therapy etc. The purpose of this qualitative study is to determine the financial needs of brain tumour patients in Ontario by evaluating publicly available data from GoFundMe, an online fundraising platform, and advocate for the creation and implementation of financial assistant programs for patients and their families in order to fulfill these needs. A series of six procedural steps outlined by Braun & Clarke's version of thematic analysis were followed. Each GoFundMe post will be read to get an overall impression of its contents, then explored line by line and/or in segments to identify and highlight codes and emerging themes. A coding framework will be created to determine emerging themes using qualitative data analysis software (NVivo 10). A sample of 195 fundraising requests from brain tumour patients were identified and analyzed. The patients and their families and friends described that the financial burdens they experience living with brain tumours and require support for include 1.) psycho-social support and accessibility during these very difficult times, 2.) basic patient financial costs and living expenses, and 3.) research and advocacy to improve overall survival and quality of life of brain tumour patients. These findings will serve as the foundation to encourage the design and implementation of interventions that aim to mitigate the financial burden experienced by brain tumour patients and their families across Ontario.

P1-H-255: At the Intersection of Neuroscience and Neuroethics for Spinal Cord Injury Research

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The clinical experience of SCI is shaped by intersecting demographic factors such as gender, race, and culture. These factors interact with neuroscience research and are directly related to patient health outcomes. As part of a major international initiative to develop novel methods to repair SCI, we explored trends and ethics themes in literature on quality of life with the goal of aligning perspectives, values and priorities with the research pathway to better represent the heterogeneity of this population. We searched Google Scholar and PubMed databases using variations of spinal cord injury and ethics. Seventy (70) papers met inclusion criteria and were categorized according to major themes identified: Coping, adjustment, acceptance (N=23); Rehabilitation and community integration (N=18); Expectations, priorities, expressed needs (N=14); Sense of self and meaning-making (N=7); and, Autonomy and

decision-Making (N=6). Using content analytic methods, we further identified 27 distinctive subthemes. Independence in the context of function and mobility, and recognition of the diversity of disability were among the most frequently coded subthemes. We found gaps in the reporting of participant demographics, particularly with race and ethnicity, location, and household income. Future neuroscience research involving the SCI community will benefit from the explicit incorporation of the voices of affected persons to capture the full range of significant and meaningful variables in data collection and maximize the benefits of ensuing findings.

POSTER SESSION 2

P2-A-256: Developmental desynchronization of calcium activity in visual cortex astrocytes

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Astrocytes control plasticity of nearby synapses via intracellular Ca2+ transients. Here, we explored the maturation of these Ca2+ signals in visual cortex layer 5 astrocytes. In acute visual cortex slices from mice postnatal day (P) 3 - 30, we targeted sulforhodamine 101-labelled astrocytes for patching using 2-photon laser-scanning microscopy. Current-voltage curves across -160 mV to +60 mV revealed two response types: a steady, time-invariant conductance, and a slowly activating component. The latter diminished with age (Spearman's rho = -0.44, $p < 0.05$, $n = 22$). Histochemistry after biocytin-loading patched astrocytes labelled more astrocyte neighbours with age ($r = 0.73$, $p < 0.05$, $n = 24$), consistent with gap-junction maturation. Astrocyte reconstructions from image stacks were used for morphometry analysis, which revealed a developmental increase in branch density close to the soma. Additionally, Sholl analysis showed that after P20, the maximal reach of astrocyte branches was reduced. Finally, we visualized spontaneous Ca2+ transients using Fluo-5F. Events within cells decorrelated with age ($r = -0.57$, $p < 0.01$, $n = 20$). Ca2+ signals also became more frequent ($r = 0.581$, $p < 0.01$) and shorter in duration ($r = -0.632$, $p < 0.01$). In conclusion, as astrocytes mature, spontaneous Ca2+ activity changes from slow synchronous cell-wide waves to brief local transients, and this was associated with maturation of astrocyte electrophysiology, gap-junctions, and morphology. This Ca2+ signal decorrelation may enable localized astrocytic control of synaptic plasticity.

P2-A-257: Integration and decoding of niche signals by adult neural stem cells

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The adult brain has a remarkable reservoir of neural stem cells (NSCs) that transit from quiescent to activated states to produce new cells. Ca2+ signaling regulates this transition, but it is unknown how distinct micro-environmental cues are decoded and integrated by NSCs through Ca2+ fluctuations. By combining sparse NSCs labeling approach, 2photon Ca2+ imaging and post-hoc immunolabeling for

multiple niche elements, we characterized the spatiotemporal dynamics of Ca2+ signals in NSCs. We found heterogeneous Ca2+ activity patterns in NSCs processes. and observed that NSCs display Ca2+ signals near rapidly proliferating transit-amplifying precursors (TAPs) that are the direct progeny of NSCs. Using super-resolution microscopy (STED), we revealed that NSCs processes are in tight contact with and in some cases bifurcates to wrap around dividing TAP. Using scRNA-sequencing and cell surface proteome analysis, we generated a communication network model of ligands expressed by TAPs and corresponding receptors expressed by NSCs. This analysis identified EphrinB1 and its receptor EphB2 as a potential pathway of communication between TAP and NSCs. We next used pharmacological approach (Ephrin B1-Fc) and optogenetic stimulation of NSCs electroporated with opto-EphB2 receptor to show that modulation of Efnb1-EphB2 pathway increases Ca2+ frequency in NSC processes. Altogether, our data indicate that NSCs receive a constant feedback input from rapidly dividing progeny through Efnb-EphB pathway that maintain a high Ca2+ frequency in NSCs, a hallmark of the quiescent state.

P2-A-258: Cadherin 4 directs the assembly of retinal circuits encoding unique aspects of dark visual stimuli

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Retinal ganglion cells (RGCs) must grow dendrites into a specific sublamina of the inner plexiform layer (IPL) to synapse with appropriate retinal interneurons and become selective for a unique visual feature such as motion, edges, etc. The molecular determinants of this important event are not entirely clear; however, our previous work suggests that members of the cadherin (Cdh) superfamily may play a critical role. By relating differentially expressed Cdhs in RGCs to their dendritic patterns, we assigned each of the 5 IPL sublamina as being positive for a specific combination of 8 Cdhs. Using histological stains and Cre-ER knockin lines, we focused on one of these candidates, Cdh4, and described that it labels a family of RGCs that targets the outer IPL sublaminae. Using dense calcium imaging methods and posthoc immunostaining, we found that Cdh4-RGCs comprise 8 RGC types and showed that each prefers a unique aspect of dark visual objects. We hypothesized that this dark object preference arises from their sublamina-specific targeting. To test this hypothesis, we repeated these studies in the absence of Cdh4 and observed that C4-RGCs fail to target appropriate sublamina and exhibit major deficits in stimulus selectivity. These results show that Cdh4 directs RGC dendrites to outer sublaminae so they can become selective for dark visual objects, and strongly suggests that Cdh expression in retinal neurons acts as a molecular blueprint for circuit assembly.

P2-A-259: A functional platform to investigate TRIO-associated neurodevelopmental disorders

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Loss- or gain-of-function mutations in the TRIO gene are associated with a spectrum of neurodevelopmental disorders (NDDs). TRIO encodes a Rho-guanine nucleotide exchange factor (RhoGEF) known to activate Rac1 and RhoA, two Rho-GTPases implicated in critical aspects of cell

migration and cytoskeletal remodelling. Recent data from our group indicate that the conditional deletion of Trio in GABAegic interneurons (INs) alters the morphological development and migration of INs, resulting in reduced cortical inhibition, autism-like behavior and epilepsy in TriocKO mice. To test whether TRIO-associated disorders results from such impairment in IN development and migration, we designed a functional validation platform to express mutant (MT) cDNA, carrying patient-derived variants, or the wild-type (WT) cDNA in explants of the medial ganglionic eminence (MGE) of e13.5 TriocKO embryos. We investigated the migration dynamics and morphological development of INs using high-resolution time-lapse imaging and quantified the 3D cell morphology using Neurolucida. We find that, contrary to the WT cDNA, MT cDNA carrying the p.E1299K or p.R1428Q mutations do not rescue the migration delay or the aberrant morphology of TriocKO INs, suggesting that these variants are loss-of-function mutations. Further assays will be conducted to test other novel TRIO variants. Furthermore, we will explore the potential impacts of these variants on RhoA and Rac1 signaling using FRET-based assays. Altogether, our preliminary results suggest that our functional validation platform is successful in evaluating the potential pathogenicity of patient-derived TRIO mutations.

P2-A-260: Distinct forms of structural plasticity of spines of adult-born interneurons induced by different odor learning paradigms

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The ability to store new information is a crucial process underlying our everyday life. This capability has been linked to modifications of the efficacy of synaptic transmission that are partly due to activity-dependent structural alterations of dendritic spines. It remains elusive whether different forms of learning and sensory stimulations induce distinct forms of structural plasticity. To address these questions, we developed a computational pipeline to reconstruct dendritic spines from confocal microscopy images into a 3D mesh model and analyzed their number and morphometric properties after distinct learning and sensory stimulation paradigms. We used simple and complex odor learning paradigms, as well as sensory deprivation known to modulate the structuro-functional properties of adult-born interneurons in the olfactory bulb. After dimension reduction and spine clustering into five populations, each population of spines showed distinct morphology. Interestingly, distinct learning and sensory stimulation paradigms involved specific forms of structural plasticity. A simple go/no-go odor learning task induced changes in morphometric properties of existing spines, without any changes in their number. In contrast, the complex go/no-go odor learning task increased the spine density and only slightly affected the spine morphology, while the sensory deprivation decreased the spine density without affecting their morphology. Our results reveal that distinct learning paradigms and sensory stimulation differently affect the number and morphometric properties of dendritic spines.

P2-A-261: Embryonic development of layer 5 pyramidal neurons: correlated spontaneous activity

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The presence of activity within embryonic pyramidal neuron (PN) circuits, in vivo, is poorly understood. To image cortical PNs in living embryos, we developed "para-uterine imaging", allowing in vivo 2p calcium imaging of somas and neurites, as well as in vivo 2p guided patch clamp recordings. In embryonic neurons transcriptomically shown to be closest to layer 5 PNs, labeled by the Rbp4-Cre mouse line, we find 2 separate phases of increased spontaneous activity: one at E14.5, and the other from E17.5 onwards, with decreased activity in the intervening transition period. Whereas the activity in somas and neurites is similar in the first phase, the activity in neurites is significantly greater than somas in the second phase. Using in vivo patch clamp recordings, we found tetrodotoxin-sensitive active conductances in all Rbp4-Cre neurons, suggesting that the activity is mediated by voltage gated sodium channels. Further, we find that spontaneous activity is correlated between neuron pairs, suggesting that there is communication between embryonic PNs. Interestingly, perturbing the embryonic activity selectively in postmitotic Rbp4-Cre neurons resulted in fine-scale changes to the laminar location of layer 5 PNs. Further, embryonic Rbp4-Cre neurons preferentially expressed autism-associated genes. Selectively perturbing 2 such genes in Rbp4-Cre neurons resulted in increased activity in the transition period. Hence, PNs form active circuits from the inception of cortex, and the activity in these circuits, which may be perturbed in autism, is involved in cortical organization.

P2-A-262: Role of microglia in inflammation-mediated disruption of neural circuit development

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Neuroinflammation initiated by maternal infection during fetal development has been strongly implicated in the etiology of neurodevelopmental disorders, including autism spectrum disorders and schizophrenia. We have shown that brief exposure of Danio rerio (zebrafish) larvae to lipopolysaccharide (LPS) causes an increase in retinal ganglion cell (RGC) branching dynamics immediately after treatment, an increase in arbor size in LPS treated animals over the following several days, and a difference in tectal neuron response to visual stimuli measured by GCaMP6s imaging, indicating an impaired visual acuity and poorer performance of LPS treated larvae in a predation assay. Delay of specification of microglia, by knockdown or mutation of the Spi1b gene, eliminates the immediate effects of LPS on RGC branching dynamics and results in an altered response profile to spatial frequency gratings, both in the absence and presence of inflammatory insult, indicating a role for microglia in the mechanisms that mediate inflammation-induced neuronal defects. We have further set up a zebrafish assay to measure prepulse inhibition, a behavioral readout that has been found deficient in schizophrenia. In addition, we have performed measurements of cell proliferation and apoptosis during early development in these experimental models. Zebrafish larvae can be genetically manipulated in large numbers, permitting rapid candidate screening in vivo. Our findings will inform translational studies that can help us better understand and potentially decrease the incidence of neurodevelopmental disorders.

P2-A-263: Glial-derived TNF mediates a component of ocular dominance plasticity to monocular deprivation

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Homeostatic synaptic plasticity is a negative feedback system that stabilizes neuronal circuit function in response to abnormal activity. This plasticity contributes to the ocular dominance plasticity observed in the developing mammalian visual cortex, which can be driven by monocular deprivation for several days. This process starts with a rapid loss in responses of binocular neurons in V1 to the deprived eye, followed by a potentiation in responses to stimulation of the open eye. The second phase of ocular dominance plasticity is based on homeostatic synaptic mechanisms and is mediated by Tumor Necrosis Factor-α (TNF). Following monocular deprivation on mice aged 26-28 postnatal days, TNF levels in the primary visual cortex were quantified to generate a daily timeline of TNF expression during developmental plasticity. Results demonstrate an increase in TNF expression levels before the second phase of ocular dominance plasticity following monocular deprivation. During this same period of time, astrocytes and microglia were investigated to identify the source of the TNF elevation following monocular deprivation. These results suggest that glial cells mediate developmental plasticity in the adolescent mouse visual cortex by increasing their TNF production upon monocular deprivation to homeostatically increase the neuronal responses to stimulation of the open eye.

P2-A-264: Specificity protein 1 is required for ephrin-mediated spinal motor axon guidance

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The intricate organization of the neural circuit is required to establish a functional nervous system. The precise guidance of axonal growth cones to their correct targets is mediated by the activation of cell-surface guidance receptors at the periphery. The axonal co-expression of ligands and their receptors appears to be a sufficient strategy to modulate the ability of receptors to respond to specific guidance signals, known as receptor/ligand cis-attenuation. A relatively simple in vivo model of neural circuit assembly is the limb trajectory of the axons of the spinal lateral motor column (LMC) motor neurons. Eph tyrosine kinase receptors and their ephrin ligands have been suggested to mediate LMC axon guidance into the limb. To further clarify the regulatory machinery of cis-attenuation, we recently identified specificity protein 1 (Sp1) expression in the LMC, and our RNA-Seq analysis demonstrated that Sp1 potentially regulated ephrin genes, thus prompting us to investigate the following HYPOTHESIS: Sp1 regulation of ephrin expression in LMC neurons controls the function of guidance receptors via cis-attenuation. We first found that the loss and gain of Sp1 function in chick LMC neurons redirected their axon trajectory with opposite effects. A neuron-specific Sp1 deletion also led to the misrouting of LMC axons in mice. In addition, Sp1 knockdown perturbed the growth preference of LMC axons against ephrins in vitro. Interestingly, the adult Sp1 mutant mice exhibited motor function defects, indicating that the precise guidance of motor axons in embryonic stages is essential for normal neuromuscular

function. Combined, our results demonstrate that Sp1 is required for the Eph/ephrin cis-attenuation-mediated LMC axon trajectory selection into the limb.

P2-A-265: The DCC/Netrin-1 System as a Target for Preventing Amphetamine-induced Alterations in Adolescent Dopamine Development

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During adolescence, the dopamine (DA) system undergoes significant structural and neurochemical changes. The DCC/netrin-1 system modulates this protracted development, with insults to this system significantly altering the maturation of the prefrontal cortex (PFC) and the behaviors that depend on its integrity. Early adolescent male mice exposed to a recreational-like dose (4 mg/Kg) of amphetamine show a decrease in Dcc mRNA in the ventral tegmental area (VTA), alterations in DA axons innervating the PFC, and impaired behavioral inhibition. In this study we investigated the effects of adolescent amphetamine exposure on DA release in the PFC and nucleus accumbens (NAc) in adulthood. We also examined if these effects could be prevented by up-regulating Dcc mRNA in the VTA using CRISPRa. Results showed that early adolescent exposure to a recreational-like dose of amphetamine led to short and long-lasting place-preference and to increased adult DA release in the NAc. Additionally, effects on PFC DA release were sexually dimorphic, only males showing exaggerated release in response to a methylphenidate challenge. Stereological analysis revealed that the DA increase in the PFC was accompanied with an increase of the DA transporter (DAT). Upregulation of Dcc mRNA in the VTA prevented the increase in PFC DA release and the development of place preference. The increase in DA release and DAT observed in the PFC of adult male mice treated with a recreational-like dose of amphetamine in early adolescence likely results from the ectopic innervation of mesolimbic DA axons to PFC.

P2-A-266: Microbe-immune crosstalk influences brain development- lessons learned from T-cell deficient mice

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The strong reciprocal symbiosis between host immunity, the gut microbiota (GM), and the nervous system facilitates their co-evolution in early life. Within the adaptive branch of the immune system, T-cells play a key role in neuroimmune signalling during development and have been implicated in various neurological disorders. In addition, T-cells are heavily influenced by GM, as demonstrated by stunted immune maturation in germ-free mice. Building on this evidence, our lab has demonstrated T-cells act as an important mediator of gut-brain communication, through a series of experiments characterizing T-cell deficient (TCRβ-/-δ-/-) mice. At a high level, these mice display atypical anxiety-like behaviour in early life and adulthood, accompanied by neuroanatomical differences in the hypothalamic pituitary axis and loss

of sexual dimorphism in limbic structures. Our current work implements 16S rRNA sequencing, quantitative gene expression, metabolomics and flow cytometry at timepoints between postnatal day 6 and adulthood to examine the developmental role of T-cells in the gut brain axis. Our results show that T-cell deficiency alters the developmental trajectory of the GM, as well as the gut and brain metabolome, suggesting a mechanism that links microbes to brain function via immunomodulatory factors. Furthermore, presence of T-cells impacts the expression of host immune genes in the gut epithelium and brain parenchyma, while temporal evolution of specific T-cell subsets aligns with developmental milestones in both GM and neurophysiological maturation. Our results demonstrate the reciprocal regulation of the gut microbiota and host immunity, and may offer key insights into the developmental origins of neurological health and disease.

P2-A-267: Characterizing radial glia-like cell populations along the hypothalamic third ventricle

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In comparison to the neurogenic zones of the lateral ventricle and hippocampus, much less is known about the hypothalamic neural stem cell (NSC) niche. In the mature hypothalamus, neural stem potential resides in tanycytes, which line the third ventricle (3V) and resemble radial glia in both morphology and gene expression. Intriguingly, tanycyte-derived neurons are thought to facilitate plasticity in the neural circuits controlling complex processes such as energy homeostasis. It remains unclear, however, whether other neural stem and progenitor populations reside alongside tanycytes that can also contribute to postnatal plasticity. Thus, here we aimed to further characterize the phenotypes of cells residing in the hypothalamic ventricular zone across development. To start, we assessed the expression of the neural stem marker Vimentin (Vim) at P14, when cell generation in the ventricular region is thought to be complete. As expected, tanycytes along the floor and ventrolateral walls of the tuberal hypothalamic 3V were Vim and extended a long basal projection; however, a small population of ventricular Vim radial glia-like cells were also observed rostrally and adjacent to the paraventricular nucleus, a region thought to be devoid of tanycytes. Consistent with this observation, single-cell RNA sequencing of the rostral-caudal hypothalamic ventricular zone at several developmental timepoints identified a Vim cluster distinct from tanycytes. This cluster was defined by genes expressed by astrocytes and/or quiescent NSCs in other brain regions. Together, these preliminary data suggested that there may be an additional radial glia-like population with neural stem potential in the hypothalamic ventricular zone.

P2-A-268: GAD1+ inhibitory interneurons mediate the emergence of organized neural networks in cerebral organoids

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Recent advances in cerebral organoid (CO) technology have allowed researchers to recapitulate the environment from which unique human cognitive processing arises. Using 60-200+ day-old human iPSC-

derived COs and live calcium imaging, we examine neural activity of the maturing human brain by capturing calcium transients from cells of the CO cortex. We observed a significant correlation between organized networks and CO maturation, with six-month COs showing the densest networks. Neuronal ensembles, groups of neurons with similar firing patterns implying functional connectivity, also appeared in larger numbers at later timepoints. Immunofluorescent stains of aged COs suggest that the observed, coordinated neural activity may correspond with distinct phases of age-dependent neuronal diversity. At 2-3 months, deep-layer excitatory glutamatergic neurons (CTIP2+) surrounded SOX2+ ventricle-like structures. At 5-months, CTIP2+ neurons were replaced with GAD1+ interneurons and SATB2+ excitatory neurons in the cortical space. To determine the impact of these cellular populations on CO network organization, we conducted live calcium imaging while treating COs with either bicuculline methiodide (GABA antagonist) or CNQX (AMPA antagonist). Network changes were only observed in bicuculline-treated six-month COs, where inhibiting GABAergic interneuron activity led to detection of higher numbers of smaller ensembles. These results imply an underlying mature CO network composed of excitatory neuron ensembles that are regulated by the silencing action of GABAergic inhibitory interneurons.

P2-A-269: A human DCC variant causing mirror movement disorder reveals an essential role for the Wave regulatory complex in Netrin/DCC signaling

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During nervous system development, neurons project axons over long distances to reach their targets and establish neural circuits. In the developing spinal cord, the axon guidance cue Netrin-1 signals through its receptor DCC to attract commissural axons to the midline. Pathogenic variants in DCC frequently lead to congenital mirror movements (CMM), a neurological disorder characterized by involuntary movements on one side of the body that mirror the intended unilateral movements on the opposite side, but how these variants impact DCC function is largely unknown. Screening of DCC in individuals with CMM recently revealed a novel variant located in a conserved motif, the WRC interacting receptor sequence (WIRS), in the cytoplasmic tail of DCC. The WIRS motif is predicted to bind to a central actin nucleation promoting factor, the WAVE regulatory complex (WRC). The WRC promotes actin polymerization, which is critical for the cytoskeletal remodeling that drives axon guidance. We show that DCC directly binds to the WRC through its WIRS motif and that the CMM-associated DCC variant has reduced binding. We find that the DCC WIRS is required for Netrin-1 mediated axon outgrowth and guidance in commissural neurons and that the CMM-associated DCC variant is a loss-of-function variant. The DCC-WRC interaction is evolutionarily conserved and is also required for Netrin-1 mediated commissural axon guidance in vivo. Together, we identify the WRC as a pivotal component of Netrin-1/DCC signaling and provide a molecular mechanism explaining how genetic variants in DCC may lead to CMM.

P2-A-270: A hyperexcitability phenotype in human stem cell derived neuronal networks of Rett Syndrome

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Rett Syndrome (RTT) is a neurodevelopmental disorder caused by a loss-of-function mutation in the X-linked gene methyl-CpG-binding protein 2 (MECP2). Using human stem cell (hSC)-derived models of RTT, researchers are investigating the reenactment of MECP2-mutant altered brain development. Previous multielectrode array research has shown hSC-derived neuronal networks exhibit patterns of activity resembling fundamental features of in vivo networks. Here, we identified a temporally complex dynamic of repetitive neural bursting that emerged early in MECP2-mutant excitatory networks, termed reverberating bursts (RB). RBs appear as a large initial activity burst across the network, followed by several high-frequency lower amplitude bursts, resembling epileptogenic activity. We found RTT networks began to reverberate earlier and in greater proportion compared to isogenic control networks - occurring between weeks 4-6. Observations of RBs marked a transition of the network from a slow to a faster network state in RTT networks. RB were abolished by the application of EGTA-AM (a Calcium chelator), but not bicuculline (a GABA receptor antagonist). The latter indicate that the mechanism of RB production likely depends on asynchronous neurotransmitter release driven by calcium. Taken together, reverberating bursts (RB) present as a temporally complex dynamic that warrants careful consideration when determining how bursts are defined. Our results show that RBs emerge early in developing neuronal networks of RTT, likely as a consequence of enhanced excitability in single neurons and networks. Early emergence of RB may be linked to disorders of hyperexcitability such as epilepsy, frequently observed in patients with Rett syndrome.

P2-A-271: Embryonic development of layer 5 pyramidal neurons: formation of functional circuits

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Layer 5 pyramidal neurons (L5 PNs) form recurrent circuits in the adult, but their cell type composition and organization during embryonic development is poorly understood. We transcriptomically identified neurons labeled by the Rbp4-Cre mouse line as embryonic L5 PNs and showed that they divide into 3 clusters, corresponding to the 3 types of adult L5 PNs (near projecting (NP), pyramidal tract (PT), and intratelencephalic (IT) types). At E14.5, all Rbp4-Cre neurons were of embryonic NP type. Other types only appeared from E15.5 onwards. Hence, the genetic composition of the developing circuitry divides into 2 phases. Similarly, Rbp4-cre neuron circuits also organized in 2 distinct phases. From E13.5 to E15.5, Rbp4-Cre neurons spanned the cortex, forming transient two-layered circuits. From E16.5 onwards, superficial layer neurons apoptosed, while neurons from the deep layer migrated to form the nascent L5. Using immuno-electron-microscopy, we identified synaptic structures on Rbp4-Cre neurons at E14.5 and E18.5. Through in vivo 2p calcium imaging, embryonic Rbp4-Cre neurons responded strongly to glutamatergic agonists, suggesting that these synapses are functional. Embryonic Rbp4-Cre neurons also

preferentially expressed autism-associated genes. Selectively perturbing 2 such genes in Rbp-4 Cre neurons resulted in ectopic superficial layers cells and an associated patchy cortical disorganization, resembling that found in autism. Therefore, our work demonstrates pyramidal neurons form circuits from the inception of neocortex, which may be involved in the etiology of autism.

P2-A-272: Floor plate derived netrin-1 is an instructive long-range guidance cue for commissural axons in the embryonic spinal cord

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The distribution and functional significance of long-range axon guidance cues remain controversial. Netrin-1 is essential for commissural axon extension to the ventral midline of the neural tube. It remains unclear, however, to what extent netrin-1 protein functions as a long-range or short-range cue in the embryonic spinal cord, nor has it been determined if netrin-1 protein has an instructive function in vivo that directs axon migration, or is merely permissive and required for axon extension. Here we address how netrin-1 protein is distributed in the developing spinal cord and how that distribution influences axon guidance. In early embryonic chick spinal cord only floor plate cells express NTN1, yet the distribution of netrin-1 protein extends ~200 µm dorsal of the floor plate, exemplary of a long-range cue. In the embryonic mouse spinal cord NTN1 is expressed by cells in the floor plate and ventral ventricular zone. We show that selective deletion of NTN1 from floor plate cells in mouse flattened the gradient of netrin-1 protein within ~200 µm of the midline and altered commissural axon trajectories across the same distance. In gain-of-function studies, we demonstrate that ectopic expression to change the distribution of netrin-1 in the embryonic spinal cord is sufficient to redirect commissural axons. These findings reveal that netrin-1 secreted by floor plate cells is distributed as a long-range cue in embryonic chick and mouse spinal cord, and demonstrate that the distribution of netrin-1 protein instructs the direction of commissural axon extension.

P2-A-273: Light-mediated planar polarization of cone photoreceptors in the mammalian retina

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In several sensory tissues, the coordinated spatial arrangement of cellular organelles within the plane of the tissue is critical to optimize detection and transmission of sensory inputs. In the mammalian retina, vision is initiated in the light-sensitive cilium of photoreceptor cells, but whether these cilia are spatially organized relative to one another in the plane of the retina remains unknown. Using 3D electron microscopy reconstructions, we discovered that the connecting cilium of cone photoreceptors is systematically eccentric and positioned on the side of the cell facing the center of the retina, thereby

defining a planar cell polarity (PCP) in the mammalian retina. We further showed that cone PCP is established around post-natal day 14, which coincides with eye opening in mice, suggesting a role for light in this process. Consistently, dark-rearing experiments showed that light is required during a critical window of development to establish cone PCP. As phototransduction is initiated by G-proteins, which are also key regulators of cell polarity, we hypothesized that light-mediated G-protein signaling might control cone PCP establishment. At the time of cone PCP establishment, we found that the G-protein signaling modulator 2 protein (GPSM2) localizes in the inner segment of cone photoreceptors and interacts with cone transducin Gαt2, a member of the Gαi family, suggesting a mechanism analogous to the one operating in the ear. Accordingly, we found that cone PCP is disrupted when Gpsm2 is conditionally inactivated in cone photoreceptors, as well as in Gαt2 null mice. Remarkably, we found that Gpsm2 null mice present visual acuity defects, suggesting a role for cone PCP in vision. These results uncover a non-canonical PCP pathway mediated by light.

P2-A-274: Identification of novel scaffold proteins in Sonic hedgehog-mediated axon guidance

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During nervous system development, axons are guided to their 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 are required for Shh-mediated axon guidance, acting downstream of Smo to activate SFKs. 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, indicating that β-arrestins act as a scaffold to recruit SFKs to Smo. We show that depleting β-arrestins or expressing dominant negative β-arrestins in commissural neurons prevent Shh-mediated axon guidance in vitro. In vivo, expressing dominant negative β-arrestins leads to defects in commissural axon guidance. My project identifies β-arrestins as scaffold proteins for axon guidance and provides insights into the molecular mechanisms underlying the formation of neural circuits.

P2-A-275: Environmental responsivity gene network moderates the impact of early life environment quality on the risk for psychopathology

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Individual differences in sensitivity to the environment can modulate the response of individuals to both a supportive and a stressful environment. This study aims at investigating functional brain networks associated with individual differences in environmental influences, and their impact on risk for psychopathology. We performed RNA sequencing of the ventral hippocampal dentate gyrus of mice exposed to two different contexts: environmental enrichment (positive environment) or chronic social defeat stress (adverse environment). Modules and central genes related to environmental responsivity were identified through a weighted gene co-expression network analysis and validated using enrichment analysis. Human single nucleotide polymorphisms from the genes of the network were weighted using the association between alleles and gene expression from GTEx and used to compute an expression-based polygenic score (ePRS). Variations in ePRS represent individual differences in the expression of the network. The ePRS moderated the association between variation in the quality of the early environment and symptoms of mania, hypomania, bipolar or manic depression (β=0.06, P=0.04), obsessive-compulsive disorders (β=0.03, P=0.03), and bipolar disorder (β=0.12, P=0.01) in adulthood (UK Biobank, N= 65542). Analysis of the gene network revealed a strong enrichment for immunological pathways. Our study identified a common mechanism involved in responsivity to environmental extremes, that informs the development of a marker that predicts the risk for psychopathological symptoms in humans.

P2-A-276: Role of mTOR/Rptor function in cortical stem cell lineage progression

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The mechanistic target of rapamycin (mTOR) signalling pathway is a central regulator that integrates intracellular signals in the developing cerebral cortex to control proliferation, differentiation, migration and dendrite formation and is thought to play a critical role in stem cell maintenance. mTOR acts through two large biochemical complexes, mTORC1 and mTORC2. Specific to mTROC1 is the regulator-associated protein of the mammalian target of rapamycin (Rptor). Here we dissected the cell-autonomous from the non-cell-autonomous role of Rptor in both cortical development and postnatal neuron maintenance. Using mosaic analysis with double markers (MADM) technologies, we generated genetic mosaics for Rptor in defined populations of cortical excitatory neurons. MADM can visualize and concomitantly manipulate genetically-defined cells in mice, providing a quantitative readout of changes in cell lineage, morphology, and function resulting from altered expression of Rptor. We observed distinct systemic phenotypes that accumulate and eventually give rise to observable embryonic microcephaly. Furthermore, we identify that Rptor is not cell-autonomously required for embryonic cortical development but instead in the maintenance and survival of defined populations of excitatory neurons. More generally, our results suggest functional relevance of mTORC1 signalling for generating overall cortical cell-type diversity.

P2-A-277: Glia-neuron communication modulates the development of circadian photoentrainment circuitry

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Intrinsically photosensitive retinal ganglion cells (ipRGCs) are critical for the photoentrainment of the body clock to the light-dark cycle, but the mechanisms regulating their development remains poorly defined. While ipRGCs are born during the embryonic period of retinogenesis, they only innervate the central pacemaker of the circadian system in the brain (the suprachiasmatic nucleus; SCN) at early postnatal stages. At the time ipRGC axons reach the SCN, the Müller glia, the main glial cell type of the retina, are generated, raising the possibility that neuron-glia interactions may be involved in shaping ipRGC development and projections. To test this hypothesis, we injected pseudotyped rabies virus expressing GFP in the SCN at P4 and analysed presynaptic partners in the retinas 8 days later. While we found many amacrine and bipolar cells in the labeled population, as expected given they are known presynaptic partners of ipRGCs, the majority of labeled cells were Müller glia, consistent with the possibility that they may play a role in regulating ipRGCs development and/or function. To investigate this idea further, we expressed tetanus neurotoxin in glial cells, rendering them incapable of calcium-dependent vesicular release upon addition of tamoxifen. When tamoxifen was injected during the first two weeks of life, the mice had an enlarged SCN innervation area and a significant impairment in photoentrainment. This work provides evidence that glia-ipRGC interaction through calcium-dependent exocytosis is critical for the development of circadian circuits, adding to a body of work placing glia as key mediators of circuit refinement and development.

P2-B-278: Loss of MDGA2 impairs NMDAR-dependent LTD during peak synaptic pruning in mouse hippocampus

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder predicated on compromised synaptic function during key periods of brain development. Modelling suggests that deficiencies in synaptic pruning, a critical process for shaping neural circuits via the active removal of synapses, may contribute to autism phenotypes. As central regulators of synapse development and function, synapse organizers may coordinate synaptic pruning at CNS synapses, suggesting that revealing their roles in this process will provide insights into mechanisms driving the onset of autism. Accordingly, we sought to determine how MDGA2, a negative regulator of glutamatergic synapse development with genetic links to autism, impacts synaptic pruning and plasticity in an autism mouse model (Mdga2+/-). We hypothesized that long-term depression (LTD), a cellular model for enduring decreases in synaptic strength, will be impaired during peak synaptic pruning due to reduced synaptic downscaling in Mdga2+/- mouse hippocampus, area CA1. Initial results suggest that NMDAR-dependent LTD is compromised in Mdga2+/- mice. This trend was observed both in dorsal and ventral CA1 slices. These deficits may underlie

established cognitive (memory) and social deficits observed in adult mice lacking MDGA2 and suggest that normalizing synaptic pruning could be a viable option for restoring synaptic plasticity dynamics in some cases of autism.

P2-B-279: Ionotropic acetylcholine receptor desensitization in neuroendocrine cells involves membrane trafficking

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Cholinergic signalling is often required to initiate long-term changes in neural activity, such as, executive attention, learning, and neuroendocrine control. The sea snail, Aplysia, reproduces when a brief cholinergic input to neuroendocrine bag cell neurons triggers a lengthy afterdischarge and egg-laying hormone secretion. Once exposed to acetylcholine, these neurons are less responsive to successive applications, and only recover after ~24 hrs, similar to the ~18-hr refractory period following the afterdischarge in vivo. To understand this prolonged desensitization, cultured bag cell neurons were whole-cell voltage-clamped. Consecutive pressure-ejections of acetylcholine at 10-, 30-, 60-, 90-, or 360-min intervals onto bag cell neurons demonstrated a uniform ~40% decrease in the 2nd current. These effects appear to be mediated by the ionotropic receptor itself, as the metabotropic acetylcholine receptor blocker, phenyl-trimethyl ammonium, failed to affect the desensitization. That stated, opening of the channel was not necessary for desensitization given that concurrent exposure to acetylcholine with the pore-blocker, hexamethonium, did not preserve subsequent currents to any greater degree than control. Moreover, pre-treatment for ≥12 hrs with the proteasome antagonist, lactacystin, lessened the desensitization to ~20%. Hence, the retrieval of ionotropic acetylcholine receptors from the membrane may underlie the extended desensitization and, thus, contribute to both the refractory period and reproductive timing.

P2-B-280: Ependymal cells assume a reactive gliotic phenotype in chronic neuroinflammation

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Ependymal cells are specialized glia that line the surface of the ventricles and spinal canal. The presence of apical cilia and intercellular junctional proteins enable the ependyma to regulate local cerebrospinal fluid (CSF) flow and establish a selectively permeable barrier between the CSF and CNS parenchyma. Ependymal cells express receptors for a variety of proinflammatory cytokines, yet the precise ependymal immune interactions that might underly cellular dysfunction in disease remain largely unexplored. Here we use single cell RNA sequencing and immunohistochemistry in a preclinical animal model of MS (EAE), and in human MS tissue, to determine the chronic neuroinflammatory profile of ependymal cells. We first confirmed the presence of ependymagliosis in EAE, as evidenced by Gfap upregulation (at both the RNA and protein level). Interestingly, other non-neuronal cell types such as fibroblasts and endothelial cells also upregulated many core gliosis genes, suggesting that they were not specific to glial reactions to injury. We therefore designed a second analysis to evaluate if there were genes uniquely upregulated by

Gfap-regulating glia (i.e., ependymal cells, astrocytes, and oligodendrocytes). This unveiled 24 genes, which defined several unique biological processes, including cilia and organelle regulation. Ciliary and junctional genes were also downregulated in ependymal cells in both EAE and MS, suggesting that functions associated with these genes may be compromised in chronic neuroinflammation. Functional studies are ongoing to determine the downstream effects of ependymal dysregulation.

P2-B-281: The role of the palmitoylating enzyme, ZDHHC9, in oligodendrocyte development and myelination

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Loss-of-function variants in the human Zdhhc9 gene have been 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. Zdhhc9 knockout (KO) mice phenocopy these white matter aberrations, displaying similar reductions in corpus callosum volume. ZDHHC9 expression in the mouse brain is also highest in oligodendrocytes and in the corpus callosum. We thus hypothesized that ZDHHC9 shapes white matter development by influencing the development of oligodendrocytes and their ability to myelinate axons. Using RNAseq and fluorescent in situ hybridization, we demonstrate that there is an increase in the number of oligodendrocyte progenitor cells (OPC) and a decrease in the number of mature oligodendrocytes in the corpus callosum of Zdhhc9 KO mice, suggesting a disruption in the maturation of oligodendrocytes. Ultrastructural analysis revealed fewer myelinated axons and decreased myelin compaction in Zdhhc9 KO mice compared to controls. These results suggest that ZDHHC9 promotes OPC differentiation and is important for myelination during development. Our preliminary data also suggest that ZDHHC9 promotes OPC differentiation and remyelination following chemical demyelination by cuprizone, suggesting that this enzyme and/or its downstream substrates may be viable targets for novel therapeutics targeting demyelinating disorders.

P2-B-282: The differential role of T-type calcium channel Cav3.2 in immature and mature dentate gyrus granule cell excitability

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Owing to their kinetics and voltage dependent properties, low voltage-activated T-type Ca2+ channels (Cav3.1-Cav3.3) underlie oscillatory electrical activity in certain brain regions. Under pathological conditions, they can play a role in the generation and propagation of epileptic seizures. Cav3.2 is strongly expressed in the dentate gyrus (DG), a region thought to be key in the development of acquired epilepsies. A current hypothesis is that the DG acts as a filter of afferent excitation, and that breakdown of this filter leads to seizures. We examined the contribution of Cav3.2 to DG granule cell (GC) excitability to understand how this channel shapes DG circuit activity under native physiological conditions. GCs are a heterogenous population with varying degrees of maturation, classified by their intrinsic

electrophysiological properties. Mouse brain slice recordings identified three types of GCs which correlated with maturational stages: immature, intermediate and mature. Using pharmacological tools and Cav3.2 knockout mice we examined the contributions of Cav3.2 in GC excitability and synaptic plasticity. We found that Cav3.2 contributed to GC excitability in a maturational stage dependent manner, where loss/blockade of Cav3.2 increased GC excitability throughout maturation. At the circuit level, Cav3.2 knockout led to deficits in mature and immature GC dependent long-term potentiation. As DG excitability is normally tightly regulated, Cav3.2 mediated changes in GC excitability may impair normal DG functions such filtering, which has implications for epileptogenesis.

P2-B-283: Actin fenestrae and osmotically-induced nanopits in rat supraoptic magnocellular neurosecretory cells.

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Osmosensory transduction (OT) in rat magnocellular neurosecretory cells (MNCs) is mediated by activation of ΔN-Trpv1 channels (N-terminal variant of the transient receptor potential vanilloid 1) via push-force applied by microtubules during hypertonicity-induced cell shrinkage (Prager-Khoutorsky et al., 2014). MNCs also express a thick layer of subcortical actin filaments which is also essential for OT, but how so remains undefined. Here we used immunocytochemistry and proximity ligation assays (PLA) with super resolution (SR) imaging (FV 3000 Olympus confocal with FV-OSR and deconvolution using constrained iterative with cellSens software) to examine the actin cytoskeleton of acutely isolated MNCs. We found the subcortical actin layer of vasopressin MNCs features fenestrae; ~0.5 µm segments of low actin density. PLA confirmed the presence of membrane sites at which TRPV1 interact with α-tubulin in MNCs (n=15) and also in osmosensory neurons of the OVLT (organum vasculosum lamina terminalis; n=101), but not in non-osmosensitive vasopressin neurons of the suprachiasmatic nucleus. Moreover, PLA did not reveal interaction sites between TRPV1 and β-actin in MNCs (n=17), suggesting channels are not linked to the actin cortex in these neurons. Interestingly, TRPV1-α tubulin interaction sites were preferentially aligned with actin fenestrae. Moreover, live-cell imaging showed that hypertonicity causes the appearance of submicron membrane pits similar in size to fenestrae in MNCs (n=30). These results suggest that actin fenestrae may favor the formation of nanodomains where the cell surface becomes indented during the early stages of hypertonicity-induced shrinkage and that OT may specifically occur at such sites within MNCs.

P2-B-284: Allopregnanolone Modulates α7 Nicotinic Acetylcholine Receptor Function and Synaptic Plasticity in the Mouse Prefrontal Cortex

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Acetylcholine (ACh) signalling via its nicotinic class of receptors (nAChRs) modulates medial prefrontal cortex (mPFC) activity and its role in cognitive circuits. The progesterone-derived neurosteroid allopregnanolone (ALLO) is produced within the brain during periods of acute stress. ALLO is well known

to exert anxiolytic effects via positive modulation of GABAergic signalling. ALLO also exerts negative modulation of nAChRs in reduced synaptosome preparations, although the mechanism and functional impact of this action is not well understood. Using whole-cell electrophysiology in acute brain slices made from adult mice of both sexes, we demonstrate that ALLO inhibits the function of α7 nAChRs located on pyramidal neurons within layer V of the mPFC. 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). While agonist activation of the mPR does not replicate ALLO's effects, blockade of PGRMC1 attenuates ALLO inhibition of α7 nAChR function. Similarly, the blockade of protein kinase C (PKC) phosphorylation activity also attenuates ALLO inhibition of α7 nAChR function. Additional endpoint experiments revealed that ALLO suppresses the expression of α7 nAChR-facilitated synaptic long-term plasticity (LTP) within this region. These findings suggest an indirect intracellular mechanism by which ALLO negatively modulates α7 AChR function within the mPFC, which may negatively impact ACh-dependent cognitive functions.

P2-B-285: Presynaptic NMDA receptors signal non-ionotropically in neocortical STDP

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Recent studies report that NMDARs can signal without Ca2+ flux. We previously found that, at inputs onto visual cortex layer-5 (L5) pyramidal cells (PCs), presynaptic NMDARs (preNMDARs) depended on Mg2+ and RIM1αβ to regulate high-frequency evoked release but signalled non-ionotropically via JNK2 to regulate spontaneous release independent of frequency. At these synapses, timing-dependent long-term depression (tLTD) depends on preNMDARs but not on frequency. We thus tested whether preNMDARs signal non-ionotropically via JNK2 in tLTD. Using quadruple patch in P11-18 acute visual cortex slices, we found that tLTD at L5 PC-PC synapses was abolished by pre- (114% ± 10%, n = 3) but not postsynaptic NMDAR deletion (71% ± 9%, n = 6, $p < 0.05$), indicating that preNMDARs control tLTD. Homozygous RIM1αβ deletion did not affect tLTD (65% ± 7%, n = 10 vs. control 62% ± 4%, n = 15, $p = 0.74$). Wash-in of the JNK2 blocker SP600125, however, abolished tLTD (96% ± 2%, n = 9 vs. control, $p < 0.001$). Consistent with a presynaptic need for JNK2, a JNK2-blocking peptide abolished tLTD if loaded pre- (96 ± 4%, n = 10 vs. control 52% ± 6%, n = 7, $p < 0.001$) but not postsynaptically (61 ± 5%, n = 12 vs. control, $p = 0.30$). In agreement with non-ionotropic NMDAR signaling, tLTD prevailed after channel pore blockade with MK-801 (69% ± 6%, n = 14 vs. control 97% ± 7%, n = 6, $p < 0.01$). We conclude that neocortical tLTD requires non-ionotropic preNMDAR signaling. Our study highlights how the textbook view of NMDARs as ionotropic coincidence detectors in synaptic plasticity needs to be reassessed.

P2-B-286: Cocaine activation of Sigma-1R depresses neuronal intrinsic excitability in the nucleus accumbens through Rab11-dependent recycling of Kv1.2 to the plasma membrane

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We previously identified Kv1.2 and Sigma-1R (S1R) protein as critical players in a dopamine-independent cocaine-induced neuronal hypoactivity in the in the nucleus accumbens shell-an adaptation that enhances cocaine reward. Understanding the mechanism through which this adaptation occurs is of the utmost clinical significance. We showed that S1R interacts with the Kv1.2 channel and that activated S1R is able to regulate the expression of this channel at the plasma membrane (PM). Using a transient expression system and cell-based ELISA assay, we first confirmed that cell exposure to cocaine increases expression of Kv1.2 at the PM when both S1R and Kv1.2 were co-expressed. Next, we performed transcriptional and translational chase assays and showed that S1R enhances Kv1.2 translation and stability. Furthermore, we found that inhibition of ER-to-Golgi trafficking pathways and the slow endosomal recycling pathways inhibits S1R modulation of Kv1.2 targeting at the PM. Given that Rab11 GTPase is involved in the slow endosomal recycling pathways, we show that S1R colocalizes with Kv1.2 and Rab11 and that Rab11-dominant negative mutant decreases Kv1.2 expression at the PM when exposed to cocaine. Because fundamental work on Rab GTPases suggest that functional impairment of Rab pathways can act as an upstream pathogenic hub in several prevalent brain disorders, elucidating how cocaine disrupts endosomal trafficking pathways will shed a new light on the neurobiological basis of cocaine addiction.

P2-B-287: Sex-dependent effects of acute stress on hippocampal synaptic function

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Stress is a global experience across all organisms, and although important for our survival, stress can have detrimental effects on brain health. More specifically, acute stress induces an intense deficit in cognitive function via the activation of glucocorticoid receptors (GRs). The activation of GRs can modify neuronal function and structure to promote lasting changes in behaviour and physiology. Despite this, the effects and precise mechanisms of stress and GR activation on synaptic function and plasticity in male and female mice remains unclear. Furthermore, how GR signalling in non-neuronal cell types contributes to the synaptic dysfunction associated with stress remains even less clear. Thus, we aim to conduct a detailed characterization of the effects of acute stress on hippocampal synaptic function in male and female mice and highlight the role of GR signalling in non-neuronal cell types in governing these effects. To accomplish this, mice will be subjected to an acute swim stress and hippocampal brains slices will be prepared for in-vitro electrophysiology. We have found that male and female mice differ in the neuroendocrine response to the acute stress. In line with this, we have also found that stress-induced impairments of hippocampal long-term potentiation (LTP) is specific to males, and unaffected in females. Currently, we are carrying out whole-cell patch clamp electrophysiology to decipher whether disruption of the excitatory/inhibitory balance in CA1 pyramidal cells contributes to the sex-dependent effects of acute stress on hippocampal plasticity. Finally, we are identifying the contribution of distinct cell types (i.e. neurons, astrocytes and microglia) in the hippocampus to the GR signalling associated with stress.

P2-B-288: Involvement of mTOR and the unfolded protein response in oligodendrocyte maturation in chronic demyelinating lesions

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Multiple sclerosis (MS) is an autoimmune demyelinating disease, that leads to neurodegeneration and permanent disabilities. Remyelination can occur during the acute phase of the disease; however, in chronic MS, remyelination declines despite the presence of oligodendrocyte progenitor cells (OPCs) within the lesions. Elucidating cellular and molecular mechanisms related to impaired OPC maturation in chronic MS can aid identifying novel remyelinating strategies. By using two models of MS in mice, the experimental autoimmune encephalomyelitis (EAE) and the cuprizone-induced demyelination, we show a transient increase in mTOR activity during the acute demyelinating stages through the downstream effector of mTORC1, pS6K, suggesting that mTOR has a role in acute remyelination. Additionally, we found an upregulation of a downstream effector of the unfolded protein response (UPR), peIF2α in acute demyelinating lesions, followed by downregulation of this marker in acute remyelination stages. In contrast, upregulated level of peIF2α persists chronically, which correlates with remyelination failure. Our direct in vitro data show that both mTOR inhibition with rapamycin and UPR induction by MS-relevant proinflammatory cytokine, impede OPC maturation and reduce morphological complexity of oligodendrocytes and normal expression of myelin basic protein. These findings are an interesting starting point to elucidate the role of mTOR and UPR pathways in regulating oligodendrocytes and remyelination in chronic MS.

P2-B-289: Zinc finger protein 179 localizes on neurite growth cones and promotes nerve regeneration following traumatic brain injury

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Traumatic brain injury (TBI) may lead to long-term behavioural deficiency, especially secondary axotomy/axon degeneration induced caused by TBI is considered as a key risk factor of the early onset of neurodegenerative diseases. We recently discovered that zinc finger protein 179 (Znf179), also known as RING finger protein 112, acts as a novel neuroprotector and interacts with sigma-1 receptor (Sig-1R). After treatment with a Sig-1R agonist dehydroepiandrosterone sulfate, Znf179 increased its interaction with various cytoplasmic proteins, annotated to functions in "Protein Synthesis" and "Cellular Movement". Interestingly, we found an obvious localization of Znf179 on neurite growth cones. Moreover, the Znf179-overexpressing transgenic mice had higher expression of genes involved in neural-regeneration compared to wild-type mice. Treatment with Sig-1R agonists used for Znf179 upregulation resulted in longer neurite outgrowth. In addition, we have known histone deacetylase 6 (HDAC6) as a binding partner of Znf179. Treatment with MPT0B291, a potent HDAC6 inhibitor, induced the association of Znf179 and the translation factors polyadenylate-binding protein-1 (PABP), which may stimulate translation initiation and promote protein synthesis. Therefore, in the study, we found that the HDAC6/Sig-1R/Znf179 pathway plays a pivotal role in axonal regeneration and functional recovery after

traumatic axotomy. Using a pharmacological strategy-induced Znf179 functions via inhibiting HDAC6 activation and altering Sig-1R signaling can facilitate intrinsic regenerative outgrowth after TBI.

P2-B-290: Characterization of cerebellar learning deficits and altered Purkinje cell physiology in a mouse model of chronic stress

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The ability to respond and adapt to stressful environments is crucial for survival. However, chronic exposure to stress causes widespread changes to neurophysiology and behaviour that are often maladaptive. The cerebellum, a critical brain region responsible for the precise coordination of movement, has been found to undergo structural and functional alterations in response to stress. Despite this, the impact of chronic stress on cerebellum-mediated behaviours, and the underlying changes to cellular physiology in the cerebellum, are not well understood. To address these questions, we employed repeated restraint as a model of chronic stress in mice. A cerebellum-dependent motor learning task, the accelerating rotarod, was used to investigate impairments in cerebellar function induced by this form of chronic stress. We found that chronically stressed mice have impaired learning in this task compared to naïve mice. To test whether these behavioral deficits correlate with alterations in Purkinje cells, the output neurons of the cerebellar cortex, we used whole-cell recordings to study their electrophysiological properties. Strikingly, we observed that the firing rate of Purkinje cells in the cerebellar vermis was significantly altered following chronic stress. These results provide a critical first step towards understanding the full extent of cerebellar alterations induced by chronic stress and the behavioural consequences associated with them.

P2-B-291: Glial cells regulate pericyte-driven capillary deficits in glaucoma

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Here, we asked whether glial cells in the retina contribute to pericyte responses by probing the mechanisms underlying capillary deficits. OHT was induced by injecting magnetic microbeads in reporter mice to visualize pericytes and/or glial cells and calcium (Ca2+) transients (GCaMP6f). Two-photon laser scanning microscopy (TPLSM) was combined with a femtomolar delivery system to image glial-pericyte-capillary responses in living mice. We used sc-RNAseq, qRT-PCR, and immunohistochemistry (IHC) to analyze molecular changes. Our findings showed reduced capillary blood flow and increased intrapericyte Ca2+ in OHT eyes compared to control (N= 9 mice/group, n= 200-376 capillaries, $p<0.001$ sc-RNAseq revealed changes in Ca2+ homeostasis pathways, including upregulation of S100B transcripts in glial cells. IHC confirmed S100B upregulation in all glial cells. Delivery of recombinant S100B protein exacerbated intrapericyte Ca2+ influx and blood flow impairment (N= 11 mice/group, n= 62-76 capillaries, $p<0.001$). In contrast, an S100B function-blocking antibody (FBA) decreased Ca2+ in pericytes

and improved capillary blood flow during OHT (blood flow-sham: 100 %, n=128 capillaries OHT + control antibody: 65 ± 19 %, n=153 capillaries; OHT + FBA: 97 ± 5 %, n=576 capillaries, N= 4-9 mice/group, p<0.001). Remarkably, S100B neutralization protected RGCs from OHT-induced death (% survival - sham: 100 %, OHT + FBA: 93%, OHT + control: 65 %, N= 11-13 mice/group p<0.001). Our results demonstrate a novel role of glial cells in regulating pericyte responses to OHT and identify S100B as a critical player in NVC deficits

P2-B-292: Visualizing live myelinic channels for a mechanistic understanding of myelin wrapping

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As oligodendrocytes (OLs) differentiate and myelinate, their processes transition from branching neurite-like structures encircling axons into multiple layers of tightly-wound membrane sheets. During wrapping, sub-micron diameter channels of cytoplasm extend from OL cell bodies throughout the developing compact myelin sheath, providing a path for organelles and metabolites to reach the distal edges of myelin and sustain its growth. Intriguingly, these channels remain after development and are thought to reopen to allow OLs to repair or replace damaged sheaths. This makes myelinic channels a potential therapeutic target in Multiple Sclerosis where OLs survive in demyelinated lesions but fail to remyelinate axons. While their exact role in myelination and underlying molecular components are not well characterized, the PI(3,4,5)P3/Akt pathway has been identified as promoting channel opening and myelin thickening. To better understand how myelinic channels form and support myelination, we have expressed fluorescent proteins in primary rodent OLs cultured on electrospun nanofibers, which OLs ensheath like axons. Using Airyscan confocal microscopy, we visualize channel and membrane dynamics at high spatial and temporal resolutions over several days of cell growth. Our findings provide insight into myelinic channel formation and dynamics, resulting from manipulating PI(3,4,5)P3 activity in cells both during and after wrapping is complete. These studies aim to understand the mechanisms that regulate the dynamic modification and regeneration of myelin in the mature nervous system.

P2-B-293: Correlated input drives population homogenization and synchronization

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Diversity exists at all scales in our world, often greatly benefitting the systems in which it exists. For many such systems, diversity is critical for robustness and stability. The brain is no different, having high degrees of heterogeneity at all scales. Interestingly, despite its heterogenous make up, brain activity has been observed to have long-term persistence. In recent years it has been shown that reductions in neural diversity are conducive to the onset of seizure-like activity, leading to a high synchrony regime and correlated dynamics. What is less clear are the contributions of correlated input to the homogenization of neuron populations. To better understand this relationship, we analyze both analytically and numerically a non-linear sparse neural network evolving over long time scales. Here we

expose the network to various levels of correlated input and examine its influence on the neural diversity expressed by the f-I curves of the population. Pursuing this metric opens up an avenue with which to explore the experimentally intractable realm of how populations of neurons may homogenize and what effect this has on their dynamics, such as the increased likelihood of seizure-like events and the overall stability of the system.

P2-B-294: A crosstalk between mTORC1 and mTORC2 is required for full retinal ganglion cell regeneration mediated by insulin

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We previously showed that insulin promotes retinal ganglion cell (RGC) dendrite regrowth after axotomy. Insulin activates the mammalian target of rapamycin complexes (mTORC1, mTORC2), but their roles in RGC regeneration are unclear. Here, we investigated role of downstream effectors of mTORC1/2 involved in insulin-mediated restoration of RGC dendrites. Ocular hypertension (OHT) was induced by injection of magnetic microbeads in Thy1-YFP mice and daily insulin eye drops started two weeks later. Synaptic regeneration was assessed by quantification of the post-synaptic marker PSD95 on RGC dendrites and co-localization with VGlut1 in bipolar cells. The role of mTOR effectors was assessed by loss-of-function approach using siRNAs against i) the mTORC1 targets S6K and 4EBP1, which are important in protein translation initiation, and ii) SIN1, a regulator of mTORC2 activity. RGC-specific protein levels and phosphorylation was assessed by flow cytometry. Insulin treatment promoted substantial dendritic regeneration accompanied by a profound restoration of post- and pre-synaptic connectivity in conditions of OHT stress. siRNA-based knockdown of mTORC1 targets showed that lack of S6K impaired insulin-mediated regeneration, while 4EBP1 silencing had no effect. Intriguingly, S6K increased mTORC2 activity through phosphorylation of SIN1, thus enhancing insulin-mediated RGC dendrite regeneration. Also, SIN1 silencing abolished insulin-mediated RGC regeneration during OHT. Furthermore, SIN1 silencing decreased the phosphorylation of Akt, a key mTORC2 target, at residues T308 and S473. This study shows that mTORC1 and mTORC2 work together to promote insulin-mediated RGC regeneration during OHT damage. Specifically, our data show that SIN1 is a key link between mTORC1 and mTORC2.

P2-B-295: Super-resolution quantification of NMDA receptor subcellular localization in health and disease

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The synapse serves as the foundation for neuronal communication and in turn healthy brain function. N-methyl-D-aspartate receptors (NMDARs) have crucial roles at the synapse and mediate synaptic plasticity. The subcellular localization of NMDAR subtypes have contrasting roles on cell health. Synaptic NMDARs promote cell-survival, whereas the overactivation of extrasynaptic NMDARs can lead to toxicity that is implicated in a variety of brain disorders. Subcellular fractionation is a common method to isolate synaptic and extrasynaptic proteins. However, NMDARs do not exist in this binary state and are

distributed at varying distances from the postsynaptic density. Here, we use the SEQUIN (Synaptic Evaluation and QUantification by Imaging Nanostructure) Star Protocol method previously described by Reitz et al. 2021 to conduct a large-scale synaptic analysis and investigate subcellular localization of NMDAR subunits. Through this approach, we have detected nanoscale shifts in NMDAR subunits that would go unnoticed using subcellular fractionation. Owning to the sensitivity of the SEQUIN method as a measure of NMDAR subcellular profiles. In recent experiments, we have detected a shift in GluN2A and GluN2B subcellular localization in the adult hippocampus. We further use the SEQUIN approach to quantify synaptic loss and various structural alterations in animal models of neurodegeneration compared to controls. The characterization of synaptic architecture is essential to gain a better understanding of the healthy synaptic state and the alterations that occur in many brain diseases.

P2-B-296: Optogenetic control of hippocampal theta oscillations dissociates memory function from hippocampal representations of space and time

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The precise temporal coordination of neural activity in the brain is thought to be fundamental for memory function. Inhibitory parvalbumin neurons in the medial septum provide a prominent source of innervation to the hippocampus and play a major role in controlling hippocampal theta (~8 Hz) oscillations. While pharmacological inhibition of medial septal neurons is known to disrupt memory, the exact role of septal parvalbumin neurons in regulating hippocampal representations and memory is not fully understood. Using calcium imaging in freely behaving mice, we first find that hippocampal neurons encode a mixture of features including location, time, and distance. We provide analytical accounts for how these representations emerge as a function of cognitive tasks. We then dissociate the role of theta rhythms in spatiotemporal coding and memory using an all-optical interrogation and recording approach. Importantly, optogenetic frequency scrambling stimulations abolish theta oscillations and modulate a portion of neurons in the hippocampus. Such stimulation decreased episodic and working memory retrieval while leaving hippocampal spatiotemporal codes intact. Our study suggests that theta rhythms play an essential role in memory but may not be necessary for hippocampal spatiotemporal representations.

P2-B-297: Tnf differentially modulates intrinsic excitability of hippocampus ca1 neurons and nucleus accumbens medium spiny neurons

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The pro-inflammatory cytokine Tumor Necrosis Factor-alpha (TNF), primarily characterized in the immune system, is known to play a role in the regulation of synaptic transmission. Glia-released TNF acts as a mediator of homeostatic synaptic scaling. At the synapse, TNF induces alterations in receptor trafficking and changes surface expression of GABA-A receptors and calcium-permeable glutamate receptors. Recent studies also suggest that TNF impacts intrinsic excitability of neurons in several brain

regions. Alterations in neuronal excitability can lead to changes in the responsiveness to synaptic stimulation, and contribute to homeostatic plasticity. In the hippocampus and ventral striatum, two regions where the role of TNF in receptor trafficking regulation is now well understood, it is still unclear whether this cytokine also impact the intrinsic excitability. In this study we investigated the impact of an acute treatment (1h) of either low (10ng/ml) or high (100ng/ml) doses of TNF on the excitability of hippocampal CA1 pyramidal neurons and medium spiny neurons of the Nucleus Accumbens (NAc). Using in-vitro whole-cell patch clamp recordings on acute slice form mice, we found that TNF treatment differentially modulates the intrinsic excitability of those two types of neurons. In the hippocampus, a low dose of TNF decreases the firing frequency of CA1 pyramidal neurons. However, in the NAc, a low dose of TNF decreases the firing rate and a higher dose increases it. Those results provide new insight into the role of TNF in adjusting neuronal function.

P2-B-298: Molecular mechanisms underlying ATP-induced Pannexin 1 homeostasis in neural cells

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The pannexin 1 (PANX1) channel and signalling hub plays key roles in neuronal development. PANX1 levels decrease with neuronal differentiation, dropping precipitously in mouse cortical neurons in the first postnatal weeks just prior to peak synaptogenesis. PANX1 is localized to postsynaptic densities where it inhibits spine stabilization and modulates synaptic plasticity. Therefore, PANX1 proteostasis likely plays an important role in neuronal development, but our understanding of this process is limited. We reported that extracellular ATP triggers PANX1 internalization in mouse N2a neuroblastoma cells. Our recent findings suggest this occurs by macropinocytosis (cell-drinking). Notably, amiloride, a macropinocytosis inhibitor, blocks ATP-induced PANX1 internalization. Additionally, a constitutively-active macropinocytosis effector, ARF6(Q67L), induces PANX1 internalization to large ARF6(Q67L)-positive macropinosome-like structures. Macropinosomes are defined by their diameter (>200 µm) and ability to take up relatively large (70 kDa) dextran-conjugated fluorescent dyes. We are using super-resolution (STED; stimulated emission-depletion) and confocal microscopy to further confirm that PANX1-positive vesicles are bona fide macropinosomes based on these properties. Together these findings support our hypothesis that PANX1 internalizes via macropinocytosis. The outcomes of this work will advance our understanding of PANX1 proteostasis in neural cells with implications for neurodevelopment and disease.

P2-B-299: Evidence for increased activation of microglia in the absence of Pink1 or Parkin

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It is likely that multiple mechanisms interact to cause the dysfunction and loss of substantia nigra and other vulnerable neurons in Parkinson's disease (PD). Growing evidence supports the hypothesis that activation of the immune system contributes to PD pathogenesis. In the brain, microglia are the main

local actors of immune responses. These cells appear to constantly probe their local microenvironment and interact with neurons through secreted factors. In PD postmortem tissue and in animal models of PD, evidence for microglial activation has been reported. Due to growing evidence suggesting the implication of PINK1 and Parkin in innate and adaptive immunity, we hypothesize that loss of function of these gene products could lead to increased activation of microglia following infections, with subsequent detrimental effects on dopamine neurons. Studying primary microglia obtained from Pink1 or Parkin KO mice, we observed that, as expected, these cells drastically change their morphology following exposure to the bacterial endotoxin LPS, switching from a polarized to an amoeboid shape. Interestingly, we observed that PINK1 or Parkin KO microglia show increased secretion of IL-6 in response to LPS and increased resilience under culture conditions when compared to WT cells. We are now evaluating the implication of such differential activation on dopamine neurons. These initial results support the hypothesis of increased innate immune responses in the brain in Pink1 or Parkin-linked PD.

P2-B-300: Guidance Receptors at Cell-Cell Junctions: Does UNC5B Reorganize Junctional Connections?

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Paranodes secure the ends of a myelinated internodes via specialized axo-glial junctions and paranodal loop-loop junctions. In the mature CNS, netrin-1 is expressed by neurons and oligodendrocytes (OLs) and required for the stability of paranodal junctions. The netrin receptor UNC5B is expressed by myelinating OLs and enriched at paranodal junctions. Mice with conditional deletion of UNC5B from OLs (UNC5B cKO) exhibit severe paranodal disorganization and reduced amounts of junction proteins, indicating that OL UNC5B is required to maintain paranodal organization. To identify candidate proteins engaged by UNC5B we used an engineered HEK293 cell line to perform a BioID protein-proximity assay. This screen identified candidate UNC5B interacting protein DLG1, a intracellular scaffold protein involved in the assembly of cell junctions that notably has been shown to regulate myelin formation. Based on homologous domains in the tight junction (TJ) protein ZO-1 and in DLG1 and UNC5B, we hypothesized that UNC5B and DLG1 might compete with ZO-1 to form "TJ-like" structures at cell membranes. Examining the relative distributions of UNC5B and ZO-1 revealed a striking lack of overlap at junctions along cell membranes. We then investigated the influence of UNC5B intracellular subdomains on the distribution of ZO-1 at TJs using ectopic expression of truncated UNC5B. Our studies aim to provide new insights into molecular mechanisms regulating cell junctions at paranodes to inform the development of new therapeutic strategies to treat demyelinating diseases like multiple sclerosis.

P2-B-301: Molecular mechanisms of dendritic membrane periodical skeleton remodeling

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Actin, an essential protein for cell architecture, development, and migration, is ubiquitously present in all cell types. Previous studies with super-resolution microscopy techniques revealed a periodical structure of filamentous actin (F-actin) rings under the membrane of axons and dendrites. Recent observations,

coupled with a weakly-supervised deep-learning imaging analysis approach, indicate that the dendritic F-actin ring structure tends to reorganize in a fiber structure during neuronal activity in dendrites but not in axons. We aim to uncover the molecular mechanisms of this structural reorganization and hypothesize that β-Ca2+/calmodulin-dependent kinase II (βCaMKII), a major decoder of Ca2+ signals in neurons, is involved. To investigate the relationship between βCaMKII and F-actin nanostructures, we are using Stimulated Emission Depletion (STED) nanoscopy in combination with F-actin rings/fibers segmentation algorithms. Since we can observe βCaMKII both in axons and dendrites, we hypothesize that it plays a differential role in regulating the F-actin cytoskeleton between these two domains. Our preliminary observations suggest that the βCaMKII intracellular distribution in axons and dendrite is different. To learn more on the dynamical interactions between the F-actin cytoskeleton and dendritic/axonal interactors, we are testing strategies to tag endogenous actin using CRISPR/Cas-9 approach, which should facilitate live STED imaging. Newly developed deep-learning methods should help optimize the live-cell imaging conditions to minimize photobleaching. Thus, the results obtained will be useful to further investigate how these dendritic patterns of F-actin regulate synaptic plasticity and the trafficking of dendritic and post-synaptic elements.

P2-B-302: Elucidating the role of microglia-derived IGF-1 in the injured and diseased CNS

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Microglia are the immune resident cells of the central nervous system (CNS). They are known to be involved in phagocytosis of cellular and myelin debris, remyelination, and formation of a neuroprotective scar in the context of injury and disease. Insulin-like growth factor 1 (IGF-1) is known to activate various signaling pathways regulating cell proliferation, differentiation, migration, and survival. As mechanisms by which microglia can repair CNS tissues remain unclear, we studied the effects of microglia-derived IGF-1 in different contexts such as spinal cord injury (SCI) and cuprizone-mediated brain demyelination. We hypothesize that IGF-1 is a key mediator of protection against demyelination, remyelination, and scar formation in these injury/disease contexts. To test this hypothesis, we produced transgenic mice whose microglia are conditionally invalidated in IGF-1 after tamoxifen treatment, namely Cx3cr1CreER::Igf1fl/fl mice. RNA-sequencing experiments revealed that genes supporting fibrotic scar formation are upregulated in conditional knockout mice after SCI. In the cuprizone model, fewer oligodendrocytes were seen in the forebrain of Cx3cr1CreER::Igf1fl/fl mice compared to their wildtype littermates 1 week after cessation of the cuprizone diet (remyelination phase). In sum, our data reveal that microglia-derived IGF-1 could regulate formation of the fibrotic and glial scars in SCI, while it may play a role in the protection and/or proliferation of oligodendrocytes in CNS demyelination.

P2-B-303: Investigating material transfer in hPSCs and hPSC-derived neurons

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Intercellular communication is an essential process by which cells exchange information regarding their environment, internal processes, and physiological needs. One of the ways this communication can happen is through the exchange intracellular cargo between neighboring cells, a process called material transfer (MT). MT can happen through the release of extracellular vesicles or through structures called tunneling nanotubes, and studies on mouse photoreceptors have shown that many different types of intercellular cargo can be transferred by MT between cells. Whether this process happens in human cells, however, is still unknown. This way, we hypothesize that MT is an important mode of interneuronal communication. Our aim is to characterize MT in 2D and 3D cultures of hPSCs and hPSC-derived neurons. To achieve this aim, we maintained co-cultures of hESCs and hPSC-derived neurons, after which cells were collected for analyses. The cell lines used in these experiments express different cytoplasmic fluorescent proteins, and the co-localization of said proteins is indicative of MT. Preliminary flow cytometry and immunohistochemistry (IHC) data indicate that MT appears to happen in both ESCs and hPSC-derived neurons, though higher in the latter, and that there is a slight increase in the proportion of cells that overgo MT the longer the co-cultures are maintained. We will continue to examine this mechanism in 3D retinal and unguided neural cultures through flow cytometry and IHC, as well as focus on investigating the mechanism behind the MT observed in these models.

P2-B-304: Atypical NMDA receptors and their effect on dendritic spine morphology in a mouse model of Huntington's Disease

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Healthy cognitive functioning relies greatly on the brain's ability to strengthen and weaken synaptic connections, known as synaptic plasticity. Dendritic spines are plastic and dynamic structures that protrude from the dendrite and are primary sites for excitatory synaptic communication. NMDA receptors (NMDARs) play an essential role in synaptic plasticity and can arrange themselves in functionally diverse configurations. Incorporation of the atypical GluN3A subunit alters the properties of classical NMDARs. GluN3A expression peaks at 1-2 weeks of age before decreasing into adulthood and is thought to inhibit plasticity by halting spine maturation giving rise to a plethora of immature spines. The consequential effects of GluN3A are implicated in various brain disorders such as Huntington's disease (HD). Deficits in synaptic connection can be seen to occur before the onset of HD symptoms and are thus a target for early detection and prevention of the disease. We demonstrate that GluN3A expression persists into adulthood in the hippocampus of HD mice and is localized at synaptic and extrasynaptic sites in which LTP experiments have shown impaired plasticity. Moreover, we showed that the persistence of GluN3A limits synaptic plasticity, thus, hypothesizing that persistently elevated GluN3A may contribute to abnormal synaptic properties in HD. We find that there is synapse loss in the hippocampus of HD mice. GluN3A expression is successfully knocked down using shRNA as confirmed with western blot, however, neither early nor late-stage knockdown rescued LTP deficits. The present study analyzes both the functional and morphological effects of knocking down atypical GluN3A in HD mice.

P2-B-305: The effect of early-life stress on lateral hypothalamic astrocytes and sleep-wake behaviours

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Astrocytes have been shown to coordinate many complex behaviours including sleep-wake cycles. Specifically, astrocytes in the lateral hypothalamus influence sleep-wake cycles via dynamic control of energy substrates to neurons across the day and night. Energetic substrate shuttling from astrocytes to neurons is significantly impaired in conditions of stress. These data led us to consider the potential role of stress-induced astrocyte dysfunction in sleep-wake disturbances, a hallmark of many psychiatric disorders. We hypothesise that stress, via elevations in blood glucocorticoids, impairs lateral hypothalamic astrocytes to influence sleep-wake behaviours. We employed an early-life stress (ELS) paradigm, which we show affects sleep-wake behaviours, significantly increases blood glucocorticoids during adolescence, and alters astrocyte morphology in the lateral hypothalamus. ELS increased nuclear translocation of astrocyte glucocorticoid receptors, which was associated with reduced expression of astrocytic proteins linked to metabolic support. We examined the impact of ELS on lateral hypothalamic-dependent behaviours to determine the role of astrocyte-specific glucocorticoid signalling in mediating stress-induced sleep-wake disturbances. To directly implicate astrocyte glucocorticoid receptors in ELS induced behavioural dysfunction we carried out stereotaxic surgeries injecting AAV2/5-GfaABC1D-Cre-eGFP into the lateral hypothalamus of glucocorticoid receptor (Nr3c1)-floxed mice. Following astrocyte-specific GR-Knock Out (KO), we observed a significant alteration in lateral hypothalamus-dependent behaviours in a sex-specific manner, without any alterations in anxiety-like behaviours or basal metabolic function.

P2-B-306: Downregulation of glutamate transporter EAAT1 as a result of endosomal mis-trafficking is involved in Christianson Syndrome ataxia and can be partially rescued with a modulator of endosomal acidification

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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 mistrafficking 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 lysosomes, and decreased in early/recycling endosomes. We observed significantly elevated glutamate levels in the cerebella of CS mice, using MALDI-MS imaging. Finally, we show that treatment with a modulator of endosomal acidification, niclosamide, via intraperitoneal injection, can rescue the mis-trafficking of EAAT1 in Bergmann glia cells, leading to partial rescue of PC loss, with potential for therapeutic intervention in CS.

P2-B-307: Extracellular acidosis modifies microglial function in neuroinflammation and stroke

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Microglia rapidly respond to changes in brain homeostasis by constantly sensing local extracellular cues. Acidification of the extracellular environment, or metabolic acidosis, is known to accompany neuroinflammation and hypoxia during stroke, conditions where fine-tuning of the microglial response is highly consequential. However, how microglia respond to drops in extracellular pH and how tissue acidosis affects microglial activity in the brain remains unclear. Here we show that reductions in extracellular pH rapidly modify microglial transcriptional signature, surveillance activity and electrophysiological membrane properties. Furthermore, acidosis induced profound metabolic adaptations in microglia and modified cytokine production in neuroinflammatory conditions. The pH-dependent regulation uncovered here also plays a major role in the microglial response to brain hypoxia. Under stroke-like conditions in vivo and in situ, microglia rapidly modified their ramified morphology, motility and damage-sensing behaviour. This process was partially driven by acidosis-induced intracellular cAMP signalling and metabolic adaptation in microglia. Taken together, our data demonstrate that extracellular acidification in the brain is not only a consequence of many neuropathological events, but plays an active signalling role in refining the complex neuroinflammatory response of microglia.

P2-B-309: IgLONs modulate synapse formation

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The synapse provides the basis for signal transmission between neurons. Various cell adhesion molecules regulate the formation of synapses by promoting the interaction between presynaptic and postsynaptic neurons. Proteins of the IgLON subfamily of the immunoglobulin superfamily have been described as regulators of neuronal outgrowth, cell adhesion, and hippocampal synapse formation. IgLONs contain three immunoglobulin domains and a glycosylphosphatidylinositol anchor. The expression of IgLONs in the cortex and hippocampus colocalizes with synaptic markers. Additionally, the homo- and hetero-dimers of IgLONs have been shown to be compatible with a model of interaction across the synaptic cleft. In this study, we identify IgLONs as modulators of cortical synapse formation. In vitro

overexpression of IgLONs in neurons increases the number of excitatory synapses while the overexpression has no effect on the number of inhibitory synapses or dendritic spines. In vitro expression of IgLONs in non-neuronal cells induces the clustering of excitatory, but not inhibitory, synaptic markers. Furthermore, IgLONs have been shown to undergo cell surface proteolysis through ectodomain shedding mediated by adamalysins and matrix metalloproteinases. In vitro expression of IgLONs in non-neuronal cells treated with adamalysin or matrix metalloproteinase inhibitor induces even greater clustering of excitatory, but not inhibitory, synaptic markers. In this study, we identify IgLONs as inducers of cortical excitatory synapse formation and their functions are regulated by ectodomain shedding.

P2-B-310: The synaptic complex igsf21-neurexin2alpha governs cortical dendritic inhibition and its disruption leads to autism-related behaviors

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Synaptic inhibition in the central nervous system is crucial for regulating neuronal activity and networks, and its dysregulation is thought to be linked with many neurological and neuropsychiatric disorders. Different populations of GABAergic interneurons regulate neuronal excitability of principal neurons in a spatiotemporal manner with dendritic and somatic GABAergic synapses constituting the two major classes of synaptic inhibition. While somatic inhibitory synapses have been extensively studied, it remains largely unknow what molecular mechanisms underlie the development of dendritic GABAergic synapses. We have previously discovered that postsynaptic IgSF21 is crucial for the development of dendritic GABAergic synapses in the hippocampal CA1 through its interaction with presynaptic neurexin2α. However, it remained unknown whether IgSF21:Nrxn2α complex also regulates dendritic inhibition in the neocortex and whether specific signalling pathways are linked to dendritic inhibition.

hrough electrophysiological recordings and immunohistochemical analysis, we have found that deletion of Igsf21 specifically impairs dendritic but not somatic inhibitory synapses in the mouse somatosensory cortex. To further explore the downstream signalling of IgSF21:Nrxn2α complex, we performed AP-MS and quantitative proteomic and isolated key candidates that regulate IgSF21:Nrxn2α synaptogenic activity. Lastly, Igsf21 deletion in mice led to defects in ultrasound vocalizations in pups as well as social behaviors impairment in adults, reminiscent of key symptoms in autism spectrum disorders.

P2-B-311: Oligodendroglial UNC5B regulates myelin modification during aging

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In the mature CNS, netrin-1 is expressed by neurons and oligodendrocytes and required for the stability of axo-oligodendroglial paranodal junctions. The netrin receptor UNC5B is highly expressed by mature oligodendrocytes. UNC5B protein is enriched at paranodes and paranodal junctions become disorganized following conditional deletion of oligodendroglial UNC5B. Here we aim to identify the contribution of

UNC5B to changes in myelin structure that occur during maturation and aging. Floxed alleles of unc5b were selectively deleted from the oligodendrocyte lineage. We then quantified internode length in wild type (WT) and UNC5B cKO young 4 month old, and aged 7 month old, mice. In spinal cord (SC) average internode length of WT and cKO animals was similar at both ages. Interestingly, while internode length shortens with age in WT SC, this age-related difference was not detected in SC of UNC5B cKO mice. Examining internode length and axon diameter in SC, young animals have longer internodes along thicker axons in WT and UNC5B cKO. SC internodes of aged WT mice have a similar profile. In contrast, aged UNC5B cKO mice do not exhibit different internode lengths for different diameter axons. Examining deep layers of the neocortex, we found that, in contrast to WT, UNC5B cKO internodes did not lengthen with age. Our findings provide evidence that the lack of oligodendroglial UNC5B is associated with a more static myelin profile with internode length less affected by age or axon diameter. We suggest that UNC5B regulates dynamic adjustments to myelin during maturation and aging.

P2-B-312: Associating Ion Channel Alternative Splicing With Neuronal Intrinsic Electrophysiological Properties Using Patch-seq

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Ion channels are thought to give rise to the molecular origins of intrinsic neuronal biophysics. These properties determine the intrinsic excitability of neurons and are responsible for the summation of synaptic inputs to axonal outputs. It is this input-output relationship that underlies all activities within the nervous system. However, the molecular basis of intrinsic excitability is highly complex, as illustrated by the sheer diversity of neuronal ion channels, proteins that are recognised as determinants of neuronal excitability. In addition, most ion channel genes are alternatively spliced to produce multiple isoforms, which can differ in a number of functional attributes, including their gating, voltage sensitivity, and intracellular trafficking. In this work, we present a novel approach in identifying alternative splicing events in ion channel genes that are correlated with intracellular electrophysiological features. We use data obtained from Patch-seq, a methodology that enables the simultaneous collection of both electrophysiological and transcriptomic features from the same cells. Using this approach, we have identified an association between the relative abundance of isoforms of the Shaw-related potassium channel gene, Kcnc1, with electrophysiological features such as firing rates and action potential widths. These relationships are consequences of the polarized targeting of the two Kcnc1 isoforms to different cellular compartments, which results in the observed alterations in biophysical properties. This example illustrates that the associations we identified using our method could potentially lead to the discovery of novel regulatory mechanisms in neuronal excitability.

P2-B-313: Vapourized cannabis transiently alleviates neuropathic pain and modulates spinal microglia activity in male rats

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Neuropathic pain is caused by injury or disease of the nervous system and is often resistant to analgesics. To alleviate pain symptoms, some patients use medical cannabis. However, the efficacy of cannabis for neuropathic pain is not well defined. In this study, we assessed the impact of vapourized cannabis exposure on mechanical allodynia in a rat model of spared nerve injury (SNI). Adult Sprague-Dawley rats underwent SNI surgery, and were exposed to a novel in-cage vapourized cannabis exposure paradigm at 7 and 14 days post-SNI. At 7 and 14 days post-SNI, we determined that vapourized cannabis exposure attenuated allodynia up to 180 minutes. Amongst the extracts tested, a combination of 10% delta-9-Tetrahydrocannabinol (THC) and 10% cannabidiol (CBD), as well as a whole cannabis extract (containing both THC and CBD) was most effective at reducing allodynia. In addition, the number of cells containing microglia markers CD11b and CD68, marking general microglia activity and their pro-inflammatory phenotype, were reduced. Combined, our data show that vaporized cannabis acutely and transiently reduces mechanical allodynia, possibly through reducing microglial activation.

P2-B-314: Vasoactive intestinal peptide-expressing interneurons differentially regulate the integration of excitatory inputs in hippocampal CA1 pyramidal cell subtypes

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The hippocampal vasoactive intestinal peptide-positive (VIP+) interneurons (INs) are highly diverse. Two main types are the cholecystokinin-expressing (CCK+) VIP+ INs and the IN-selective (IS) VIP+ INs. While CCK+/VIP+ INs inhibit the pyramidal cells (PCs), the IS INs disinhibit the PCs by suppressing particular IN types. The PCs are in turn composed of two major types: deep (dPC) and superficial (sPC). Whether and how the VIP+ INs modulate the activity of both PC types remains elusive. Here, using light-activation of VIP+ INs, we found that VIP+ INs provide monosynaptic inhibition to both PC types. Next, using chemo-silencing of VIP+ INs, we found that integration of both the temporoammonic (TA) and the Schaffer collateral (SC) inputs by PCs was coordinated via VIP+ INs. Especially, during TA stimulation, both dPCs and sPCs increased inhibitory postsynaptic responses (IPSPs) following VIP+ IN inactivation, in line with VIP+ IN-mediated disinhibition in the CA1 area. In contrast, during SC stimulation, only dPCs increased IPSPs after VIP+ IN silencing, while sPCs revealed higher excitatory PSPs suggesting an additional VIP+ IN-mediated shunting effect on SC input integration. We also tested TA and SC integration in PCs while light-activating VIP+ INs. In brief, we saw lower dPCs-IPSPs and higher sPCs-IPSPs during TA and SC stimulation, respectively. Together, these data suggest that VIP+ cells in the CA1 area are involved in both inhibitory and disinhibitory circuit motifs and provide a cell type-specific mechanism for coordinating the integration of excitatory inputs.

P2-B-315: Histamine stimulates human microglia-derived cells and alters prion protein expression

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Background: Prion protein (PrPC) has a neuroprotective role in the central nervous system (CNS) albeit through unclear mechanisms. Interestingly, PrPC is expressed in microglia, which are innate immune cells

of the CNS that are involved in both neuroprotection and neuroinflammation. We proposed that PrPC might influence human microglial responsiveness to different stimuli. Lipopolysaccharide (LPS) is known to stimulate microglia, but literature also suggests that histamine induces the release of inflammatory mediators and alters protein expression in murine microglia. We tested the effects of LPS and histamine on human microglial response and correlated this with PrPC expression. Methods: qPCR was used to confirm the expression of histamine receptor mRNA. Cytokine and chemokine production were measured by ELISA and electrochemiluminescence multiplex assay. Surface and total PrPC protein expression were measured via flow cytometry and western blot. Results: Histamine caused upregulation of histamine receptors on human microglial clone 3 (HMC3) cells and induced increased production of IL-6 and IL-8 in a different pattern than LPS. Surface PrPC expression was also altered following histamine stimulation, in a time- and dose-dependent manner. Conclusions: Our data show, for the first time, that human microglia express histamine receptors, are activated by histamine, and that histamine alters the expression of PrPC. Future experiments will test whether PrPC is necessary or sufficient to directly mediate microglia response.

P2-B-316: Pharmacological characterization of neonicotinoid-sensitive cholinergic receptors in identified molluscan neurons

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Neonicotinoids activate nicotinic-type acetylcholine receptors in insects, although they may impact non-target species. For example, exposing the pond snail, Lymnaea stagnalis, a food-web intermediary abundant in North America and Europe, to field concentrations of the neonicotinoid, imidacloprid, proves lethal. To study the neurophysiological basis of this mortality, we examined the effect of imidacloprid on Visceral Dorsal 1 (VD1) and Right Parietal Dorsal 2 (RPD2), a pair of electrically coupled central neurons that are essential for cardio-respiratory function. Prior work showed that applying acetylcholine to VD1 and/or RPD2, under sharp-electrode current clamp in the isolated brain, caused depolarization. We now find that imidacloprid did not mimic this effect, but instead served as an antagonist of the acetylcholine response. Depolarization was elicited by the nicotinic agonist, tetramethylammonium, whereas the muscarinic agonist, arecoline, produced only hyperpolarization. Moreover, the muscarinic antagonist, phenyltrimethylammonium, not only failed to eliminate the depolarization but extended the duration of the acetylcholine response. Interestingly, the nicotinic receptor pore-blocker, hexamethonium, also did not antagonize the depolarization, perhaps due to voltage-dependent relief. Overall, acetylcholine likely acts through a depolarizing nicotinic-type receptor, which is tempered by a hyperpolarizing muscarinic-type receptor. If imidacloprid interferes with this cholinergic input to VD1/RPD2, it may compromise cardio-respiratory control and survival.

P2-B-317: Regulation of axonal plasticity by panglial networks

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The axon initial segment (AIS) is a highly specialized compartment of the proximal axon that facilitates the initiation and propagation of action potentials (APs) and regulates neuronal polarity. Recent studies have shown that this structure is not static, as has always been assumed, but undergoes plastic changes in its length and location in a homeostatic regulation. Although these phenomena have been recently described in several studies, the mechanisms responsible for them are still poorly known and understood, but there is increasing evidence that glial cells contribute to them. Near the AIS and along the axon, oligodendrocytes and astrocytes coexist and can couple together to form networks called panglial. Our previous work has shown that local calcium decreases increases neuronal firing by enhancing a sodium persistent current and can be produced by release of an astrocytic calcium-binding protein. Using electrophysiological recordings, we found that prolonged stimulation of primary afferent neurons located in the brainstem, or of Layer 5 pyramidal neurons, produced by repeated applications of BAPTA (a calcium chelator) along the AIS cause a long-term increase of excitability of the recorded cells and that this change in excitability was prevented by blockade of astrocytic networks. These preliminary results suggest that panglial networks contribute to plastic changes in the AIS and to the modulation of APs propagation along the axon.

P2-B-318: Matching heterogeneous presynaptic inputs with postsynaptic excitability to expand coding capacity of principal neurons

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Synapses are tuned to convey a wide spectrum of information necessary for sensory perception and cognitive processing. At each synapse, the integration of presynaptic input to generate postsynaptic action potentials (APs) determines transmission fidelity. At the mature calyx of Held synapse in the auditory brainstem, it is well-established that calyx terminals with simple morphologies (mainly stalks) have smaller quantal output and express short-term depression, whereas structurally complex calyx terminals (stalks and numerous bouton-like swellings) have larger quantal output and express short-term facilitation. Consequently, postsynaptic spiking fidelity during afferent nerve stimulation is low in simple calyces, and high in complex calyces. However, whether diverse postsynaptic excitability contributes to this morpho-functional continuum is not known. Using morphological tracing and whole-cell patch-clamp recordings, we discovered simple calyces tend to innervate postsynaptic neurons with a phasic firing pattern (firing a few APs at onset of current injection). In contrast, complex calyces are more likely to innervate postsynaptic neurons with a tonic firing pattern (repetitive firing of APs until end of current injection). The variability of intrinsic excitability among postsynaptic neurons diversify the fidelity and pattern of neurotransmission in response to prolonged stimulations. Thus, postsynaptic neurons are tuned to match heterogeneous presynaptic inputs by design, working synergistically to expand the dynamic range of coding signals. Supported by CIHR and NSERC

P2-B-319: Role of GluN2D NMDA receptor subunits in the hippocampal CA1 region of Fmr1 knockout mice

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Fragile X Syndrome is the most prevalent form of inherited intellectual disability and commonly studied using Fmr1 knockout (KO) mice. Changes in hippocampal synaptic plasticity have been reported in KO mice. In hippocampal slices two forms of NMDA receptor-dependent synaptic plasticity, short- and long-term potentiation (STP and LTP), are co-induced by theta-burst stimulation (TBS). STP is the initial potentiation, which exponentially decays upon synaptic stimulation, while LTP is the stable enhancement of synaptic transmission (LTP). STP has not been examined in Fmr1 KO mice. Four induction paradigms (3, 5, 10 and 30TBS) were used to investigate STP and LTP in the CA1 region of hippocampal slices from 8 - 10-week-old control and KO mice. Similar to previous studies, KO mice showed deficits in LTP induced by weak induction paradigms (3 and 5TBS), but not the longer 10TBS protocol. Interestingly, for the extended 30TBS protocol, both STP and LTP were decreased in the KO mice. Synaptic potentiation induced in hippocampal slices is dependent on the activation of specific NMDA receptors subtypes. In Fmr1 KO mice the role of GluN2A and 2B subunits have been widely studied. However, the role of GluN2D subunits, which are involved in the induction of STP, has not been studied in KO mice. Thus, we examined sensitivity to the novel GluN2D-preferring antagonist UBP791 using the 30TBS paradigm. Preliminary data show a trend for increased UBP791 sensitivity of LTP in the KO. If confirmed, the findings would implicate a role for GluN2D in synaptic function of Fmr1 KOs.

P2-B-320: Deletion of FMRP dysregulates mGluR5 and Homer trafficking

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Fragile X Syndrome (FXS) is the most common inherited form of intellectual disability and a leading genetic cause of autism spectrum disorder (ASD) caused by transcriptional silencing of the FMR1 gene that encodes the Fragile X messenger ribonucleoprotein 1 (FMRP). In the mouse model of FXS, Fmr1 knockout (KO), excessive signaling of group 1 metabotropic receptor (mGluRs) was found to exaggerate long-term depression (LTD, a well-established cellular model implicated in learning and memory) and ASD behaviors, all of which can be rectified by double knockout of FMRP and mGluR5, or deletion of short-form Homer-1a. However, it remains elusive how these key elements dynamically interact during early-phase of mGluR signaling. We addressed this by investigating the redistribution of mGluR5, FMRP and Homer1 in slices of cerebellum and auditory brainstem from WT and Fmr1 KO mice following application of Group I mGluR agonist DHPG, and further examined these reciprocal relationships by high-resolution imaging of fluorophore tagged mGluR5, FMRP and Homer1b expressed in CHO cells. We found much more mGluR5 and Homer are colocalized near the membrane of neurons from Fmr1 KO than WT. Their colocalization is increased in WT but reduced Fmr1 KO neurons following DHPG treatment. The increase can be recapitulated in CHO cells co-expressing all three elements. Our findings implicated the critical role of FMRP in mGluR5 and Homer trafficking for the early induction of synaptic

plasticity, independent of its canonical role as mRNA translational repressor in regulating protein translation.

P2-B-321: The role of cerebellar synaptic heterogeneity in Purkinje cell function

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The cerebellar cortex is known for its homogeneous circuit architecture, which repeats across lobules. Yet, this region can support a multitude of diverse functions, raising the question of how this homogeneous circuitry can support heterogeneous functions. Recent studies indicate heterogeneities in synaptic plasticity and gene expression across the cerebellum. However, whether and how baseline synaptic transmission itself varies across the cerebellum remains unknown. Here, we focused on Purkinje cells (PCs), the output neurons of the cerebellar cortex, each of which receives information from tens of thousands of parallel fiber (PF) input synapses. Using patch-clamp electrophysiology from acute mouse cerebellar slices we measured excitatory glutamatergic, metabotropic glutamate receptor (mGluR)-dependent currents at PF-PC synapses. Surprisingly, we discovered a marked heterogeneity in these currents across different cerebellar lobules. As a consequence, PC firing in response to PF synaptic input was markedly different. Furthermore, this heterogeneity was correlated with the differential expression of splice variants of the canonical Transient Receptor Potential channel (TRPC3), which acts as a downstream effector of mGluRs. Thus, our results demonstrate a remarkable, and previously undiscovered, heterogeneity in excitatory synaptic transmission in the cerebellum; a finding that has significance for how functionally different cerebellar regions process incoming information in very different ways.

P2-B-322: Conditional deletion of syngap1 in nkx2.1-expressing mge-derived interneurons decreases excitability and ampa-mediated thalamocortical input onto parvalbumin-positive interneurons in mouse auditory cortex.

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SYNGAP1 haploinsufficiency-related intellectual disability (SYNGAP1-ID) is characterized by moderate to severe ID, generalized epilepsy, autism spectrum disorder and other behavioral abnormalities. We have recently found that auditory sensory processing and associated neuronal oscillations in the gamma band are altered in SYNGAP1-ID patients and Syngap1 haploinsufficient mice, however the underling cellular mechanisms are currently unknown. To investigate the impact of Syngap1 deletion on synaptic and intrinsic properties of layer IV parvalbumin expressing (PV+) cells in the adult auditory cortex in vitro, we generated mice that were heterozygous for the Syngap1flox allele and hemizygous for the Tg(Nkx2.1-Cre) transgene. Intrinsic and synaptic properties of PV+ cells were examined using whole-cell current and voltage clamp recordings respectively. We found that Syngap1 haploinsufficiency in PV+ cells had no impact on their synaptic properties, but decreased their intrinsic excitability affecting the action potential threshold, rheobase current and firing frequency. Further, the AMPA component of

thalamocortical evoked-EPSC was decreased in PV+ cells from mutant mice. Taken together, these data suggest that Syngap1 haploinsufficiency in PV+ cells leads to decreased intrinsic excitability and thalamocortical AMPA component, which in turn could lead to a reduced recruitment of PV+ cells. The latest could contribute to the increased baseline cortical gamma rhythm, a phenotype observed in both Syngap1 haploinsufficient mice and SYNGAP1-ID patients.

P2-B-323: Distinct roles of pre- and postsynaptic NMDARs in synaptic release and plasticity

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In the textbook view, postsynaptic NMDA receptors (postNMDARs) serve as detectors of coincident pre- and postsynaptic activity in Hebbian plasticity. However, mysterious presynaptic NMDARs (preNMDARs) have also been found. Here, we explore the roles of pre- and postNMDARs in synaptic release and plasticity. Immunogold electron microscopy in P21 C57BL/6 mice revealed GluN1, 2A, and 2B subunits pre and postsynaptically at primary visual cortex (V1) layer 5 (L5) excitatory synapses. GluN2B dominated over 2A presynaptically, and 2A over 2B postsynaptically ($p<0.001$), in agreement with prior electrophysiology studies. Next, we generated a sparse NMDAR deletion model by neonatal injection of AAV9-eSYN-mCherry-iCre-WPRE in NR1flox/flox mice. Using quadruple patch in P10-19 acute slices, we recorded pyramidal cell (PC) pairs with NMDARs deleted pre- (preKO) or postsynaptically (postKO). We verified deletion with MNI-NMDA uncaging (postKO: 0.3 pA ± 0.4 pA, n=16 vs. control -26.7 pA ± 4.7 pA, n=28, $p<0.001$). AP5 failed to suppress EPSPs in PC-PC pairs with preKO (102% ± 8%, n=7), yet successfully did with no or postKO (pooled: 49% ± 9%, n=10; $p<0.001$), indicating that pre- but not postNMDARs control short-term plasticity. Moreover, in pairs with preKO or pre- and postKO deletion, tLTD was abolished (114% ± 10%, n=3), but not for postKO or control (71% ± 9%, n=6, $p<0.05$), showing that tLTD needs pre- but not postNMDARs. Our study shows how pre and postNMDARs differentially affect synaptic release and long-term plasticity. The textbook view of NMDAR function may thus need to be revised.

P2-B-324: Cellular and network mechanisms of CACNA1A gain of function associated epilepsy

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CACNA1A mutations causing a gain of function (GOF) of the CaV2.1 calcium channels are typically associated with familial hemiplegic migraine type 1 (FHM1). However, we recently described de novo GOF variants leading to Lennox-Gastaut syndrome. The mechanisms by which these variants induce epilepsy rather than FHM1 are unclear. We generated a novel mouse model carrying an epilepsy-associated GOF mutation (Cacna1aA713T+/-) to explore these mechanisms. Cacna1aA713T+/- mutant mice display an increased mortality (50%) before P21. Survivors have smaller body weight, diffuse tremors, ataxia, spontaneous seizures of various types. Further, they display impulsivity, hyperactivity

and deficits in spatial learning and memory. An increase in the amplitude and frequency of both spontaneous glutammatergic and GABAergic synaptic transmission was recorded in cortical layer V pyramidal cells from somatosensory cortex of mutant mice. However, a loss of cortical parvalbumin expressing interneurons, most strikingly in layers IV and V, and a reduction of layer V somatostatin expressing interneurons was observed. This loss of INs was confirmed by Nkx-RCE fate mapping which revealed a significant reduction of the total density of GFP expressing INs. In summary, the epilepsy-associated A713T mutation induces a clinical phenotype reminiscent of Lennox-Gastaut syndrome and, contrary to what has been described in FHM1 models, it affects both pyramidal cells and GABAergic INs, with striking facilitation of synaptic release from both populations and a preferential impact on interneuron survival.

P2-B-325: Connectivity and activity correlates of an anomalous excitatory neuron subtype in the subiculum

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Our lab has recently identified a sparse population of excitatory neurons that occupies the deepest layer of the subiculum, the main output region of the hippocampus. Our research here investigates the connectivity and activity correlates of this unique cell subtype, referred to as "deep cells". To do so, our lab has generated a new transgenic mouse line that allows cre-mediated cell-type-specific access of these deep cells. Utilizing this transgenic line with cell-type-specific viral tracing tools and whole brain clearing, we discovered that this deep cell population exhibits unique morphological properties compared to other subiculum excitatory neurons. Images of whole intact axonal projections revealed that deep cells form dedicated projections to the ventral and medial components of the anterior thalamic nuclei, a region involved in aspects such as spatial working memory and attention. Additionally, concurrent in vivo imaging data from our lab has revealed that these cells exhibit sustained activity responses after encounters with novel objects. Motivated by this, along with the unique local and long-range structure of these neurons, we utilized fluorescent in situ hybridization to identify activity correlates and potential preferential recruitment of deep cells following a novel object recognition task. In sum, our data provides evidence for a previously unknown excitatory cell subtype within the subiculum that exhibits unique structural characteristics, and could play a potentially specialized role in recognition memory.

P2-B-326: Regulation of axonal transport in neurons by protein palmitoylation

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Neurons are large, complex cells requiring efficient trafficking and delivery of neuronal proteins and organelles to specific subcellular locations. Fast, continuous transport of cargo along axonal microtubules by dynein and kinesin motors is critical for neuronal function and requires a constant source of energy. Interestingly, glycolytic enzymes were recently found tethered to fast moving vesicles to provide an 'on-

board' energy supply directly to the molecular motors. The activity of motor proteins is tightly regulated, and aberrant activity can result in neurodegeneration or neurodevelopmental deficits. One important mechanism to dynamically regulate protein trafficking in neurons is the covalent addition of fatty acids to protein cysteines residues, a process known as palmitoylation. Interestingly, glycolytic enzymes as well as several kinesin and dynein motor subunits and their activators have been identified in high throughput palmitoyl-proteomic studies as potentially palmitoylated. Thus, we hypothesize that palmitoylation tethers multiple motor proteins, their activators, and glycolytic enzymes to vesicles to provide 'on-board' energy and continuous movement required for fast axonal transport. Indeed, we have recently confirmed that glycolytic enzymes as well as p150Glued, a subunit of the dynein activating complex dynactin, are palmitoylated in neurons and, interestingly, their palmitoylation regulates their vesicle association and axonal localization. These findings provide insight into the molecular mechanisms that govern fast axonal transport with implications for neurodevelopment, synaptic function, and axon degeneration.

P2-B-327: On demand recruitment of presynaptic kainate receptors promotes the development of facilitation onto somatostatin interneurons

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Short-term facilitation of excitatory inputs onto somatostatin (SOM) interneurons results in a delay in the recruitment of SOM inhibition. Facilitation is enhanced by the expression of presynaptic GluK2-containing kainate receptors (GluK2-KARs). We find that synaptic inputs to SOM neurons in layer 2/3 (L2/3) of mouse barrel cortex show increases in synaptic facilitation and GluK2-KAR expression during the first few postnatal weeks. The removal of sensory input early in development with whisker trimming prevents the emergence of presynaptic GluK2-KARs, which can be restored by allowing whisker regrowth or by calmodulin activation. Conversely, late trimming or acute inhibition of CaMKII is sufficient to reduce GluK2-KAR activity. This on demand regulation also produces a specific reduction of L4 GluK2-KARs that develops in parallel with the maturation of sensory processing in L2/3. Thus, the dynamic regulation of presynaptic GluK2-KARs provides a means to flexibly scale SOM interneuron mediated late inhibition.

P2-B-328: High dietary salt amplifies constitutive cell proliferation and adult neurogenesis in sensory circumventricular organs

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Adult neurogenesis proceeds through adulthood in the subventricular zone and hippocampal subgranular zone. Median eminence (ME) and adjacent medio-basal hypothalamus, two hypothalamic regions controlling energy balance, are additional areas containing neural stem cells (NSCs) that give rise to new neurons and glia in the adult brain. The ME is one of the circumventricular organs (CVOs), which are specialized brain areas featuring an incomplete blood-brain barrier, thereby mediating crosstalk between the central nervous system and the peripheral circulation. Additional CVOs located in the

hypothalamus are the Organum Vasculosum of Laminae Terminalis (OVLT) and the Subfornical Organs (SFO). The OVLT and SFO contain neurons which are activated in response to increased blood osmolality and sodium, thereby playing a central role in the regulation of hydromineral balance, thirst, and autonomic and cardiovascular functions. Whether the OVLT and SFO harbor adult NSCs remains unclear. Here, we demonstrate the existence of constitutive cell proliferation in the OVLT and SFO of adult rats. We show that NG2 glia, tanycytes, and pericytes proliferate in these CVOs. The OVLT and SFO also contain populations of newborn neurons, which can differentiate and express mature neuronal markers. Importantly, we show that the proliferation of glia cells and the generation of newborn neurons are amplified in rats fed high salt diet. These findings show that adult glial proliferation and neurogenesis persist in the OVLT and SFO and the rate of these processes is modified by diet-induced changes in the hydromineral balance, potentially contributing to the regulation of body fluid homeostasis.

P2-B-329: Calcium buffering tunes intrinsic excitability of spinal dorsal horn parvalbumin interneurons: A computational model

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Parvalbumin-expressing inhibitory neurons (PVINs) play a crucial role in the dorsal horn of the spinal cord in preventing touch inputs from activating pain circuits. After nerve injury, their output is decreased via mechanisms that are not fully understood. We showed that PVINs from nerve-injured mice change their firing pattern from tonic to adaptive. To examine the ionic mechanisms responsible for this decreased output, we employed a reparametrized Hodgkin-Huxley (HH) type model of PVINs, which predicted (1) the firing pattern transition is due to an increased contribution of small conductance calcium-activated potassium (SK) channels, enabled by (2) impairment in intracellular calcium buffering systems. Analyzing the dynamics of the HH-type model further demonstrated that a generalized Hopf bifurcation differentiates the two types of state transitions in the transient firing of PVINs. Importantly, this predicted mechanism holds true when we embed the PVINs model within the neuronal circuit model of the spinal dorsal horn. To experimentally validate this hypothesized mechanism, we used pharmacological modulators of SK channels and demonstrated that (1) tonic firing PVINs from naïve mice become adaptive when exposed to an SK channel activator, and (2) adapting PVINs from nerve-injured mice return to tonic firing upon SK channel blockade. Our work provides important insights into the cellular mechanism underlying the decreased output of PVINs in the spinal dorsal horn after nerve injury and highlights potential pharmacological targets for new and effective treatment approaches to neuropathic pain.

P2-C-330: Sex- and age-dependent transcriptional responses early after ischemic stroke in mice

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Ischemic stroke is a well-recognized disease of ageing that disproportionally affects men, yet age- and sex-dependent cellular mechanisms remain understudied in the literature. Emerging animal studies

support the role of neutrophil activation and stalls in the microvascular as a potential contributor to poor clinical outcomes. Using the murine middle cerebral occlusion (MCAO) model that mimics a vessel occlusion with recanalization, we performed a comprehensive microarray analysis of blood samples after ischemic stroke in male and female, and young adult and aged mice 3-6-months old and 18-24 months old, respectively. Three experimental groups (N=46), including sham, 1-hour MCAO, and MCAO with 3-hour recovery post-reperfusion, were examined. Blood samples were collected upon euthanasia 60 minutes after surgery, except for the reperfusion group, where the occlusion was removed after 60 minutes, and mice were to recover for 3 hours before euthanasia. Total RNA was extracted from blood samples and analyzed using Affymetrix Clariom S Assay. All expression analysis was performed in RStudio and Bioconductor. The limma package was used to identify differentially expressed genes across sex and age in response to injury ($|FC| \geq 1.5$, p-value≤ 0.05), topGO, GSEA, and Qiagen IPA were used for functional enrichment analysis. We uncovered new genes and their functional pathways distinct to treatment groups, ages, and sexes. Notably, Vcan and Ngp are upregulated at the 3-hour MCAO mark in old animals and female animals only. These analyses identified new transcriptomic targets to modulate neutrophil activation that may contribute to poor outcomes after stroke. Future studies will probe manipulations of these genes using high-resolution in-vivo 2-photon imaging of microvascular dynamics.

P2-C-331: Tau pathology in the lateral entorhinal cortex-dentate gyrus circuit affects memory and morphological plasticity

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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 used an inducible cre-recombinase transgenic mouse model to label neurons born at different ages (development vs. adulthood) with TdTomato, and an AAV injection either expressing wild-type human Tau or a control vector 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 assessed 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 (LEC-dependent) compared to healthy controls, while no difference is found for NPR (hippocampal-dependent). Morphological results show that both developmentally- and adult-born neurons have an increase in thin dendritic spines and decrease in mushroom spines in tau animals relative to controls, as well adult-born neurons have decreased dendritic length and complexity.

P2-C-332: Evidence of mitochondrial DNA instability in late-onset major psychosis

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Background: Bipolar disorder (BD) and schizophrenia (SCZ) are highly heritable diseases with overlapping symptoms and there is evidence supporting mitochondrial involvement in both diseases. The present study aimed to characterize the mitochondrial DNA (mtDNA) variants toward early vs. late onset in individuals diagnosed with BD and SCZ. Methods: We analyzed the whole mitochondrial genome using next-generation sequencing from 89 individuals (44 BD and 45 SCZ), age 27-72, 49.5% female. The mtDNA-Server workflow was used for mtDNA variant analysis, and functional analysis was performed by Mutserve. Individual variants were tested with the phenotypes using logistic regression in R, and a Bonferroni correction was applied. Correlation analyses were used to investigate the associations between heteroplasmy levels and early vs. late onset BD and SCZ. Results: Logistic regression analysis showed no significant association of mtDNA common variants with diagnosis. The global heteroplasmy level was significantly higher in SCZ when compared to BD (p=0.032). Comparing early vs. late onset, the global heteroplasmy level was significantly increased in late-onset SCZ individuals when compared to BD (late-onset (p=0.048) and early-onset (p=0.027)), and no difference was found when compared to early-onset SCZ (p=0.073). Correlation analysis showed significant associations between age and both the number of heteroplasmy variants and global heteroplasmy level (r=-.219, p-value=0.039; r=-.282, p-value=0.007, respectively). Conclusions: Our findings showed that higher heteroplasmy levels are revealed in late-onset schizophrenia individuals. Further studies in other populations are required to support these findings.

P2-C-333: Regulation of localisation and function of ER-resident chaperone GRP78 by palmitoylation in glioblastoma multiforme

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Glioblastoma multiforme (GBM) is the most common adult malignant brain tumor with poor prognosis and devastating neurological symptoms. GBM is resistant to conventional treatments so new approaches are critical. A promising target is the unfolded protein response (UPR) which is activated by unfolded and misfolded proteins in the ER. The Hsp70 chaperone GRP78/BiP (HSPA5) is the central modulator of UPR and normally resides in the ER. However, with strong UPR induction it mislocalises to the cell surface where it enhances signaling pathways associated with GBM drug resistance and malignancy. Importantly, targeting cell surface GRP78 with antibodies decreases GBM malignancy. How GRP78 trafficks to the cell surface and is anchored there is unclear. One potential mechanism to tether soluble proteins to membranes is the protein modification palmitoylation. Thus, I hypothesize that palmitoylation of GRP78 anchors it at the cell surface where it promotes GBM proliferation. Using click chemistry, I found that GRP78 is palmitoylated in U-87 MG glioblastoma cells and that UPR dramatically enhances GRP78

palmitoylation. Furthermore, treatment of U-87 cells with a broad palmitoylating enzyme (PAT) inhibitor prevents UPR-induced palmitoylation. This suggest that GRP78 is palmitoylated by PATs and that palmitoyl-GRP78 is likely abundant in the cell surface fraction. Future work includes locating GRP78 palmitoylation sites, establishing which PATs palmitoylate GRP78, and investigating how palmitoylation contributes to GRP78 localisation and cell proliferation in various GBM models.

P2-C-334: Purinergic regulation of injury-induced neurogenesis in the adult Danio Rerio

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In contrast to mammals, adult zebrafish (Danio rerio) undergo successful neural regeneration following spinal cord injury (SCI). Radial glia lining the zebrafish central canal function as neural progenitors that undergo a massive injury-induced 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 SCI is the purinergic signaling system. While purines such as ATP and its metabolites mediate diverse cellular processes within the mammalian central nervous system (CNS), their roles have not been explored within the zebrafish CNS. Given that the purinergic system is evolutionarily conserved among vertebrates, we sought to characterize potential roles for P2X7 and P2Y2 receptor signaling in neurogenesis following SCI in adult zebrafish. Our findings demonstrated that expression of P2X7 and P2Y2 receptors were upregulated following injury, and activation of P2X7 signaling, in particular, enhanced injury-induced neurogenesis in this species. Further work will elucidate the roles of both receptors in these natural regenerators following SCI.

P2-C-335: Endolysosomal changes and BDNF-TrkB signaling deficits in spinocerebellar ataxia type 6

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Spinocerebellar ataxia type 6 (SCA6) is a genetic disorder presenting with mid-life onset motor coordination impairment and late cerebellar degeneration. Using a mouse model of SCA6 (SCA684Q/84Q() that displays deficits in motor coordination at 7 months, we previously identified aberrant cerebellar BDNF-TrkB signaling, where both BDNF and TrkB are reduced in cerebellar Purkinje cells, as a contributor to SCA6 pathophysiology. However the cause of this signaling reduction is currently unknown. Our RNA-Seq data suggested that components of the endolysosomal system are altered in SCA6 mice, so we investigated whether endolysosomal dysfunction was observed and if it was, whether it contributes to BDNF mis-trafficking in SCA6. We carried out immunohistochemistry with markers for endosome compartments in the cerebellum of SCA6 mice. We found that in the Purkinje cells of SCA6 mice, early but not recycling endosomes were enlarged. Purkinje cell lysosomes appear morphologically normal but RNA-Seq data showed an upregulation of lysosomal enzymes, suggesting an increase in lysosomal activity in the SCA6 cerebellum. Interestingly, we observed that BDNF was elevated in early endosomes in Purkinje cells in SCA6 tissue, suggesting that it is mislocalized in intracellular compartments. Taken together, these results suggest that the endolysosomal system is altered in SCA6

cerebellum, and that the previously characterized reduction in BDNF-TrkB signaling in SCA6 may be due in part to mislocalization of BDNF in endosomal compartments.

P2-C-336: Ketogenic interventions alter liver gene expression and cytoarchitecture in the 3xTg model of Alzheimer's disease

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Ketogenic dietary interventions have shown promising clinical results in the elderly population having in mild cognitive impairments, a population at high risk for developing Alzheimer's disease (AD). Ketogenic interventions likewise improve performance of AD mouse models in tests of cognitive function, suggesting this is an appropriate model to investigate underlying mechanisms. Since our preliminary results showed that AD mice develop liver-associated peripheral metabolic abnormalities (Poster by Mbra et al.), we investigated the impact of ketogenic interventions on the liver transcriptome and cytoarchitecture in the 3xTg model of AD. Mice were administered either a standard carbohydrate-rich diet (SD, 70% carbohydrate, 20% fat, 10% protein), an identical diet except that a portion of the fats were replaced with ketogenic medium-chain triglycerides (kMCT), or an extreme carbohydrate-free ketogenic diet (KD). Bulk RNA sequencing of the liver revealed that untreated 3xTg mice exhibit more than 800 dysregulated genes compared to their control strain. About 11% of these genes are involved in the metabolism of ketone bodies and lipids, and their expression is partially or totally restored by kMCT or KD diets. Preliminary observations of liver histology indicate that untreated WT and 3xTg mice exhibit baseline differences in morphology and lipid droplet localization, and that KD and kMCT diets differentially affect hepatic morphology. These findings suggest that AD pathology may involve alterations in a liver-brain axis that can be modulated by ketogenic interventions.

P2-C-337: Stabilizing post-stimulation oscillatory dynamics by engaging synaptic plasticity with tACS

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Non-invasive brain stimulation techniques (NIBS), either electrical or magnetic, became important practical tools in neuroscience. The oscillatory behavior of the brain due to the synchronous activity of neurons plays a vital role in brain functions, and modification in its power through NIBS has shown promising therapeutic interventions for neurological and neuropsychiatric disorders. Despite extensive studies on their effectiveness and the variability in the outcomes observed in experiments, it needs to be better understood how these techniques alter neural circuitry to modify brain function. Such variability can be explained by the complex interactions between induced electric fields and neuronal responses, further complicated by the heterogeneous properties of neural tissue. In this study, we explored the effects of transcranial alternating current stimulation (tACS) on a synchronous cortical circuit in several circumstances that lead to elevated post-stimulation oscillatory activity. We studied the influence of heterogeneity in neuron time scales on the post-stimulation epoch in a population of leaky-integrated

and fire (LIF) neurons that exhibit synchronous-irregular activity. Our results indicate that heterogeneity in neurons' time scales is essential to induce persistent post-stimulation effects. We reasoned that this persistent effect is a consequence of selective synaptic modifications resulting from the diversified response of heterogeneous neural populations. Additionally, we explored the importance of synaptic plasticity among and between excitatory and inhibitory to excitatory neurons in the modulation of post-stimulation power.

P2-C-338: Wake/sleep architecture and electrocorticographic activity in two rodent models of Alzheimer's disease

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In Alzheimer's disease (AD), sleep alterations are among the first clinical symptoms observed. It is also well-established that sleep loss affects hippocampal function. Mounting literature indicate that soluble amyloid-beta oligomers (Aβo) are particularly neurotoxic and their specific contribution to sleep disturbances remains to be defined. Recently, dysregulation of lipid metabolism was reported in AD and 3xTg mice but its relation to sleep also needs to be assessed. Therefore, our work has two objectives: define the effect of Aβo on different sleep variables, and verify whether stearoyl-coA desaturase (SCD), an enzyme involved in lipid metabolism, contributes to sleep disturbances in 3xTg mice. Chronic hippocampal injections of soluble Aβo were done in male rats, and electroencephalographic (EEG) measurements were performed to define wake/sleep alterations. Additionally, female 3xTg mice received a 28 day-treatment with an SCD inhibitor, and EEG recordings were performed either 14 or 28 days post-treatment. Results show that the time spent in wakefulness, slow-wave sleep (SWS) and paradoxical sleep was preserved in Aβo-injected rats. However, EEG spectral activity 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 during SWS for theta (5-9 Hz) and alpha activity (9-12 Hz). Moreover, the theta activity/SWA ratio was decreased during wake and SWS. Concerning 3xTg mice, they spend more time in SWS during their active period compared to littermates. Ongoing analyses will assess the impact of SCD on sleep variables in 3xTg mice. The results support the presence of sleep alterations in AD models and suggest that sleep phenotypes could serve as a non-invasive marker of early AD.

P2-C-339: α-synuclein preformed fibrils bind to β-neurexins and impair β-neurexin-mediated presynaptic organization

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In synucleinopathies, including Parkinson's disease, several fundamental questions remain unanswered, notably regarding the mechanisms underlying the binding and internalization of α-syn to mature neurons. The hypothesis for a trans-synaptic α-syn propagation is growing interest because of two reasons: 1) synaptic structures are the first affected during the early stages of the disease progression and 2) the majority of the endogenous α-syn necessary for the disease progression is located at presynaptic sites. Therefore, highlighting synaptic protein candidates that might help the entry of α-syn into the neuron seems to be promising to prevent such internalization. Neurexins (NRXs) are important presynaptic adhesion molecules that regulate synaptic properties and transmission. My current study has revealed that neurexin-1β (NRX1β) is able to interact with α-syn through its unique N-terminal histidine-rich domain (HRD). Moreover, I calculated the dissociation constant (KD) for this interaction in cell-based and cell-free assays and found a KD of ~500nM. Consequently, I hypothesized that NRX1β is a key molecule for the entry of α-syn into neurons. I am 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. In parallel, our laboratory has developed a unique transgenic mouse model expressing NRX1β without its HRD and developing Parkinson's disease to assess the role of NRX1β HRD in vivo.

P2-C-340: Pharmacokinetic profiling of TD874, a small molecule inhibitor of SOX9 and a potential new strategy to reduce CSPG levels in the injured spinal cord

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Chondroitin sulfate proteoglycans (CSPGs) are extracellular matrix proteins that are increased in the central nervous system following injury and found to inhibit regeneration. Our laboratory has identified SOX9 as a transcription factor that upregulates several genes involved in CSPG synthesis. We have also shown that conditional SOX9 ablation reduces CSPG levels at the lesion site and improves locomotor recovery after spinal cord injury (SCI) in mice by increasing the reparative sprouting of spared axons. The present project aims to identify small-molecule inhibitors of SOX9 for possible clinical translation for SCI. Since SOX9-driven transcription of extracellular matrix genes has been shown to be dependent on SOX9 dimerization, we carried out a computational screen to identify small molecules predicted to interfere with SOX9 dimerization. Several candidates were identified and one designated ZO2, was shown to reduce CSPG levels in vitro. In addition, intrathecal administration of Z02 to spinal cord injured rats reduced CSPG expression in the injured cord. A library of Z02 analogs was generated to identify Z02 analogs with improved pharmacokinetic properties. We will report the pharmacokinetic properties of one Z02 analog, TD874. TD874 has a half-life of approximately 1 hr when delivered to rats iv and good blood-brain barrier penetration. We will report on TD874's pharmacokinetic profiling including its stability in the rat's injured spinal cord. Our intention is to develop TD874, or other Z02 analogs in our pipeline, for preclinical testing in spinal cord injured rats.

P2-C-341: Spatial transcriptomics reveals regional, cellular, and molecular dysregulation following traumatic brain injury

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Traumatic brain injury (TBI) is known to cause inflammation, vascular and white matter damage of varying severity. Additionally, repeated TBI has been found to increase risk of dementia onset later in life. Despite extensive research into the pathophysiology of TBI, the underlying mechanisms responsible for these pathologies are still undetermined. In order to better interpret TBI-induced pathologies, we employed a data-rich approach to examine the molecular changes occurring in a murine TBI model with spatial transcriptomics. Using the non-surgical Closed Head Impact Model of Engineered Rotational Acceleration (CHIMERA) paradigm, we were able to reliably reproduce biomechanical, behavioural, and neuropathological TBI phenotypes in cFosTRAP mice. Then, by utilizing the Visium spatial transcriptomics platform, we investigated gene expression differences between TBI and sham mouse brain samples. Through our analysis of these datasets, we identified a diverse group of region-, and cell-type-specific transcriptomic changes as a result of TBI dysregulation. To further validate these results, we performed multiplexed in situ hybridization and immunohistochemistry against differential targets extracted from our dataset. The results from this study have the potential to be transformative in how we understand the brain-wide, molecular and cellular changes which occur following TBI. Furthermore, our results could deliver clinical insight into prospective biomarkers and therapeutic targets for detecting and treating TBI, with the goal to improve patient outcomes.

P2-C-342: Role of LRRK2-G2019S mutation in neuroinflammatory pathways

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We are interested in the interaction between genetic risk and inflammatory environmental triggers in the development and progression of Parkinson Disease (PD). LRRK2 gene variation and mutations confer the highest genetic risk for familial PD, and LRRK2 mutations cause typical, late-onset PD, which is clinically indistinguishable from the idiopathic disease. LRRK2 has been widely associated with inflammation and immune cell function, while it is still unclear the effects of LRRK2 mutation on inflammatory response outside of immune cells, particularly in neurons. This work explores the effects of the most common LRRK2 mutation (G2019S) in the regulation of immune signaling onto neurons. We describe experiments in LRRK2-G2019S knock-in (GKI) mouse neuronal primary cultures treated with pro-inflammatory triggers - IFNy and LPS. Our initial results suggest alterations in endo-lysosomal markers and lysosomal damage in GKI neurons upon immune stimulation, which might be induced by inflammasome activation. The data establish a framework to interrogate the impact of LRRK2-G2019S mutation in balancing an immune response with neuronal function and survival through the complex mitochondria/lysosome axis. With better understanding of how gene mutations and inflammatory stimulation predispose the brain to neuronal dysfunction and degeneration in PD, we hope to uncover new target pathways for the design of novel interventions and ideally neuroprotective strategies for this and related diseases.

P2-C-343: Ouabain-na+ /k+ atpase signaling induces IL-2/IL-10-dependent neuroprotection of axotomized retinal ganglion cells

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The death of retinal ganglion cells (RGC) underlies vision loss in several retinal diseases. Yet, no pharmacological treatments exist to prevent these neurons from dying. Previous work demonstrated that the Na+/K+ ATPase ligand ouabain (Oua), interleukin (IL)-2, and IL-10 have neuroprotective effects on axotomized RGC. Given that Oua is an immunomodulatory hormone, we hypothesized that ouabain's neuroprotective effects are mediated through an IL-2- and IL-10-dependent mechanism. We treated primary cultures from rat retina with Oua for different times and measured levels of IL-2, IL-2 receptor, and IL-10 by Western Blotting. To identify cell types expressing IL-2/IL-10, we performed immunofluorescence double staining against IL-2/IL-10 and Brn3a (a RGC marker). To evaluate cell survival following optic nerve axotomy, RGC were retrogradely labeled in vivo with HRP, and quantitative analyses of RGC survival were performed after treatment in vitro with Oua and/or antibodies against IL-2 or IL-10 for 48h. Oua modulated the synthesis and secretion of IL-2 and IL-10 and the expression of its receptors in retinal cells in a time-dependent manner. In addition, 50% of positive Brn3a+ RGC express IL-2 or IL-10, and Oua treatment significantly modulated IL-2 and IL-10 expression in these cells. Furthermore, Oua treatment prevents axotomized RGC death, for at least 48h, through an IL-2/IL-10-dependent mechanism. Overall, these findings suggest that Oua modulates retinal IL-2/IL-10 signaling, which is crucial to restore cell homeostasis and protect RGC following optic nerve axotomy.

P2-C-344: Age-related neuronal changes are alleviated by dietary restriction in part through the regulation of neuronal architecture maintenance molecules

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Cognitive decline during aging is well-known in humans, however the mechanisms by which neuronal dysfunction is triggered during aging are poorly understood. Using C. elegans, which has greatly contributed to studies of the nervous system and of aging, we systematically surveyed age-related neuronal changes, extending previous studies. We found neuron-type specific structural alterations, across the entire nervous system, during normal aging. These changes are uncoupled from lifespan extension, as they were not delayed in several long-lived mutants. In contrast, age-related neuronal alterations were a robustly delayed in calorically restricted animals (using the model eat-2 mutants, which ingest little food). To dissect the molecular pathways behind the neuroprotective effect of caloric restriction, we determined that the transcription factor pha-4/FOXA is required for maintaining neuronal organization during aging, similar to its requirement for eat-2 mutants' long life. The neuronal maintenance gene sax-7 is a potential target of PHA-4/FOXA and its expression level is upregulated in calorically restricted animals. Moreover, increasing sax-7 level largely could preserve neuronal organization in otherwise normally aging animals. SAX-7's mammalian homolog is L1CAM, which has both neurodevelopmental and postdevelopmental functions during adulthood to preserve cognition.

Given the conservation between the human and C. elegans, the genes that halt or promote neuronal decline in C. elegans will help uncover the principles underlying neuronal aging and neurodegenerative diseases.

P2-C-345: Targeting the NF-kB pathway as a therapeutic strategy for maintaining motor neuron connectivity in a mouse model of ALS/FTD-FUS

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative diseases that belong to a common disease spectrum. While the underlying causes of ALS/FTD are still under investigation, dendritic attrition and loss of synaptic densities are recognized as early pathological markers of disease. However, the sequence of events that lead to these changes remain unclear. Fused in sarcoma (FUS), an RNA-binding protein with known genetic and pathological links to ALS/FTD, has important functions in the maintenance of neuromorphology and synaptic connectivity. ALS/FTD animal models expressing FUS variants have behavior defects along with dendritic attrition of motor neurons and loss of synapses, but the mechanisms by which FUS variants cause these changes remain unclear. We show that neuron-restricted expression of the ALS-linked FUSR521G variant in mice causes age-dependent defects in cognitive and motor function that coincide with dendritic attrition and synaptic loss. We demonstrate that cognitive impairments in juvenile mice correspond with dendritic attrition of cortical motor neurons, which later progresses to the spinal cord, resulting in dendritic attrition of the spinal motor neurons and motor impairments in adult mice. Importantly, we show that glial activation, FUS mislocalization and defects in mitochondria only occur in symptomatic adult FUSR521G/Syn1 mice. Using a therapeutic approach, we demonstrate that inhibiting the NF-kB pathway in ALS-FUSR521G mice restores cognitive and motor function as well as increases dendritic branching and synapses. These findings have helped elucidate the role of FUS in synaptic health and dysfunction and identified strategies to treating synaptic dysfunction associated with ALS/FTD.

P2-C-346: Investigating altered sensory function in a peripheral organoid model of autism spectrum disorder (ASD)

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Altered sensory processing is a key clinical feature of autism spectrum disorder (ASD), with indication of both central nervous system and peripheral nervous system (PNS) involvement. Evidence from genetic ASD models demonstrated that altered sensory system development (e.g., mechanosensory neurons) contributes strongly to sensory and behavioural deficits. Several ASD risk genes including Fragile X messenger ribonucleoprotein 1 (FRM1), Cytoplasmic FMR1 interacting protein 1 (Cyfip1), and Serine/Threonine-Protein Kinase TAO2 (TAOK2) have been implicated in mRNA translational regulation, a critical process in ASD affecting neuronal plasticity. In this project, we will use human pluripotent stem

cell (hPSC) models to model sensory deficits linked to ASD. We have generated 3D human dorsal root ganglia-like organoids (DRGOs) previously shown to recapitulate key aspects of PNS development. Using this model we will generate DRGOs from isogenic FMR1, CYPIF1 and TAOK2 KO hPSC lines to examine the cellular basis of PNS sensory dysfunction, with an emphasis on mRNA translation control. We hypothesize that altered function in human sensory neurons is influenced by altered local translation and contributes directly to sensory deficits in ASD. Preliminary brightfield and immunocytochemistry data suggest early deficits in FMR1 KO DRGOs compared to WT controls. We are currently working to examine the molecular/cellular basis underlying these phenotypes via immunohistochemistry, single cell RNA sequencing, and network functional assays using assembloid and in vivo transplantation studies.

P2-C-347: New links in fatty acylation , proteostasis deficiency, and ALS

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Protein mislocalization and proteostasis deficiency are hallmark features in neurodegeneration. Initially, mutations lead to protein mislocalization, decreased protein turnover, aggregation, and ultimately cell death. Aggregation cannot be easily reversed and has been shown to not be a tractable target in neurodegeneration. Translocation is one of the first steps in pathology. To this end, as protein mislocalization is likely more readily reversible than protein aggregation, understanding the mechanisms regulating subcellular localization of disease proteins will be critical for therapy development in neurodegeneration. Thus, dynamic S-palmitoylation provides a unique and targetable link between mislocalization and proteostasis deficiencies in the pathogenesis of neurodegeneration. Previously, our unbiased bioinformatics approach found that the top diseases predicted to be dependent upon S-palmitoylation included ALS amyotrophic lateral sclerosis (ALS), TDP-43 proteinopathies, and proteostasis deficiencies. Our lab is focused on identifying and characterizing S-palmitoylation proteins involved in neurodegeneration, particularly in ALS. To date, we have identified several proteins linked to ALS, and their co-factors, that are S-palmitoylated. We are currently characterizing how S-palmitoylation of these proteins are regulated and how fatty acylation is affected in disease models including yeast, fly, patient cells, and mice.

P2-C-348: Anterograde and retrograde propagation of tau between the hippocampus and entorhinal cortex in mice

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Tau pathology is one of the main neuropathological markers of Alzheimer's Disease (AD), and correlates closely with neurodegeneration and cognitive decline of the patients. Tau propagates in a stereotypical manner in AD, spreading from the entorhinal cortex (EC) to the hippocampus during the early stages. To date, much of the work examining tau propagation has been performed using mutated tau and/or transgenic animal models. Since tau is not mutated in AD, the main objective of this study is to evaluate the anterograde and retrograde propagation of non-mutated tau in a mouse model. Tau preformed fibrils (2 µg) of small size (50-200 nm), or a vehicle solution are injected in the hippocampus or in the entorhinal cortex in 2-month-old C57BL/6J mice. Mutated P301L tau is also injected to determine if there is variation of propagation between mutated and non-mutated tau. Tau propagation is evaluated at different time points following single or chronic injections (24 h after one injection, or 24 h, 1, 5, 9, 13 weeks after 5 consecutive days of injections). The levels of propagation and neurodegeneration are determined using an anti-tau (AT8) and anti-NeuN staining. Because the mechanisms of tau propagation have not yet been fully elucidated, and because tau is known to propagate before becoming hyperphosphorylated and forming large aggregates, examining the propagation of small, non-mutated fibrils of human tau in a wild-type mouse model will give unprecedented information on how tau can influence neurodegeneration and cognitive decline in the early stages of AD.

P2-C-349: SIRT3 as a Disease-Modifying Agent in Parkinson's Disease

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Mitochondria dysregulation is central to the pathology of Parkinson's disease (PD). The Sirtuins (SIRTs) (subtypes 1 -7) are a family of protein deacetylases and ADP-ribosyltransferases linked with enhanced longevity and cytoprotective function. Sirt3 is the major mitochondrial protein deacetylase involved in the regulation of oxidative stress and metabolism. We previously showed that intra-cerebral administration of the gene therapy, AAV.SIRT3 has neuroprotective effects in a pre-clinical rat model of PD. The current studies were performed to further validate SIRT3 as a disease-modifying gene therapy for PD. Given that increasing age is the primary risk factor for PD, and SIRT3 expression declines with age, we first tested whether SIRT3 expression is decreased in the brains of parkinsonian subjects compared to age-matched controls. In PD subjects, there was a significant reduction in SIRT3 levels compared to age-matched controls (56.83±15.51%, $P<0.01$), suggesting that decreased SIRT3 may be linked to the progression of PD pathology. Since our previous studies showed that stereotaxic delivery of AAV.SIRT3 has disease-modifying effects, we assessed whether less invasive methods for enhancing SIRT3 have similar beneficial effects in rodent models of PD. AAV.SIRT3 was non-invasively delivered using MRI-guided-Focused Ultrasound, and effects on motor function and dopamine cell number were quantified. We also assessed the disease-modifying effects of hexa-fluro Honokiol, a synthetic derivative of is a naturally occurring compound found in magnolia officinalis, which has previously been shown to increase endogenous SIRT3. These studies will show whether non-invasive enhancement of SIRT3 expression has the ability to rescue motor function and dopamine cell death.

P2-C-350: Modeling epileptic Dravet syndrome using patient-derived brain organoids

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The first line treatment for Dravet syndrome is a three-drug combination that offers partial seizure relief in ~50% of the patients, leaving half of Dravet children without treatment options. We propose that other combinations of anti-seizure medications (ASMs) might be effective but with >450 potential combinations, it is unclear which ones. We created iPSCs from a Dravet individual and her parent as an isogenic control for use in growing brain organoids. To accurately model epilepsy, we created individual dorsal and ventral forebrain organoids and fused them together to generate brain 'assembloids'. The Dravet assembloids were smaller in size and showed a decrease in the number of neuronal progenitors compared to controls. Concomitantly, the Dravet assembloids displayed an increase in excitatory neuron populations. Interestingly, the bioenergetics profiles were dysregulated in the Dravet assembloids and our electrophysiological recordings showed that Dravet assembloids display seizure-like hyperexcitable events. Collectively, our data suggest that neural progenitors in Dravet brains tend to exit the cell cycle faster, leading to misspecification of excitatory neurons and neurometabolic compromise. Further

analyses of the scRNA-seq dataset from patient and parent assembloids is ongoing for better understanding of disease etiology and to potentially uncover novel druggable targets. Next steps are to screen ASM combinations to identify those that restore bioenergetics to baseline levels in the patient assembloids and then test these combinations back in the donor child.

P2-C-351: Using patient-derived hiPSC microglia to characterize LRRK2 signalling in Parkinson's disease

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Autosomal dominant mutations in the gene encoding dual function kinase and GTPase, LRRK2, are the most common genetic cause of Parkinson's disease (PD) and increase kinase activity in vivo. While the function of LRRK2 is unknown; there is evidence that it plays a role in immune function, and it is highly expressed in microglia. LRRK2 is known to phosphorylate a subset of Ras analogue in brain (Rab) GTPases. This work aims to explore LRRK2 signalling in microglia and how it contributes to PD pathogenesis. Human induced pluripotent stem cell (hiPSC) lines, including a control, LRRK2 KO, LRRK2 G2019S and isogenic correction have been differentiated into hiPSC-derived microglia-like cells (iMGs). Expression of LRRK2 and phosphorylation of its target Rabs has been confirmed in iMGs. Stimulation of iMGs with inflammatory agents increases LRRK2 expression, and phosphorylation of LRRK2-target Rabs. Of the inflammatory stimuli tested, treatment of iMGs with interferon γ (IFNγ) elicits the greatest increase in LRRK2 expression and Rab phosphorylation. Whole transcriptome RNA sequencing analysis was performed on unstimulated and IFNγ treated iMGs. Analysis of differentially expressed genes (DEGs) is ongoing. Identifying DEGs between LRRK2 KO, WT and G2019S iMGs will shed light on cellular pathways affected by LRRK2 activity in microglia, and the involvement of LRRK2 in determining the state of microglia on the continuum from resting to reactive. This work will increase understanding of the pathogenesis underlying, and the role of inflammation and microglia in, LRRK2-associated and sporadic PD.

P2-C-352: N-terminal Acetylation of synuclein slows down pathology development in mice

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Alpha-synuclein (aSyn) is a ubiquitous protein in the brain, aggregation of this protein is linked to several diseases including Parkinson's disease. Under physiological conditions aSyn can undergo post-translational modification, the type of modification may affect how aSyn aggregates and becomes toxic. For instance, phosphorylation or glycation of aSyn could promote the formation of aSyn inclusion in mice and in vitro, whereas N-terminal acetylation on aSyn has been found to inhibit the pathological process of aSyn aggregation in vitro. It is presently unknown whether this reduced propensity to aggregate in vitro translates into reduced toxicity in vivo. To address this question, we generated unmodified and N-terminally acetylated preformed aSyn fibrils (PFFs and NTAc-PFFs) and injected them into mice in an established paradigm for studying aSyn-induced neurodegeneration. Electron microscopy

characterization showed that both forms of the PFFs had similar size, but the Thioflavin T kinetic assay revealed that the NTAc-PFFs recruited less aSyn monomer compared to control PFFs, suggesting that NTAc reduced the propensity of PFFs to promote aggregation. Moreover, M83 transgenic mice overexpressing human A53T aSyn, injected with NTAc-PFFs survived longer compared to M83 mice injected with control PFFs. Our findings reveal that the N-terminal acetylation both reduces the propensity of aSyn to aggregate and attenuates PFF toxicity in vivo. We propose that a deeper understanding of the regulation of aSyn NTAc might help us to clarify the process of aSyn aggregation in patients.

P2-C-353: Traumatic brain injury and cholinergic dysfunction as determinants of Alzheimer's disease susceptibility in a humanized mouse model

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Objective: To assess the role of mild cholinergic dysfunction in the development of Alzheimer's-like pathology and cognitive deficits following repetitive mild traumatic brain injury in a next-generation humanized transgenic mouse. Methods: Mice carrying humanized versions of two proteins implicated in Alzheimer's pathology, amyloid precursor protein and tau and carrying vesicular acetylcholine transporter knockdown (VAChTKD) to induce a mild cholinergic deficit will be used. Mice will 3 repetitive closed head mTBIs (mild traumatic brain injuries, one a day for 3 days) at 6 months of age. At 6 months and 12 months post-injury attention will be assessed via the touchscreen rodent continuous performance task (rCPT). Additionally, histological and biochemical analyses of Alzheimer's-related pathological changes (amyloid and tau aggregation, cholinergic loss, neuroinflammation and neurodegeneration) will be performed. Results to date: Both male and female VAChTKD show mild reductions in discrimination sensitivity at baseline when attentional demand is increased on the rCPT. At 6 months post-mTBI, injured VAChTKD females showed decreased discrimination sensitivity relative to wildtype injured animals at the shortest stimulus duration. No effect of injury or VAChTKD was observed in the males at 6 months post-injury. Conclusion: in this mid-way point in the study, discrimination sensitivity is reduced on rCPT only in females that have both a cholinergic deficit and a history of mTBI. Pathological investigations and one-year post-mTBI behavioural studies are still underway.

P2-C-354: The Effect of Neuroinflammation and Cell Death on the Electrophysiological Properties of Spikes and Local Field Potentials in the Ascending Visual Pathway of Danio rerio

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Pannexin-1 (Panx1) channels have been implicated in neuroinflammation and may play roles in balancing cell death and cell survival, but details of the molecular and cellular mechanisms are lacking. Here, the acute treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to was used to induce neuroinflammation in a zebrafish model. Changes in locomotor behavior, electrophysiological properties of the ascending visual pathway, and transcriptome changes of wild-type Tupfel longfin and panx1a

knockout zebrafish larvae were correlated with a depletion of dopaminergic neurons and neuroinflammation. Cell death following acute MPTP treatment was visualized by acridine orange staining and in-vivo imaging. The main loss of neurons was found in the pallium and tectum. The neuronal loss correlated with decreased locomotion; the phenotype was rescued by treatment with the NLRP3 inflammasome inhibitor INF39. Dual recordings of local field potentials from the optic tectum (OT), amygdala (DM), and hippocampus-like structure (DL) demonstrated that MPTP caused PD-like changes in power spectral density of ß-waves and γ-waves and in the coherence between brain regions when Panx1a was depleted; wild type larvae with Panx1a had the opposite effect. A basic spike analysis revealed a modulation of waveforms when Panx1a was depleted. Further, MPTP treatment decreased the waveform variability. Both the LFP and spike analysis support a contribution of Panx1a to the modulation of neuronal networks under conditions of neuroinflammation.

P2-C-355: Understanding the molecular mechanisms of toxicity from nuclear alpha-synuclein

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A growing body of evidence suggests an accumulation of nuclear aSyn plays a role in the pathogenesis of Parkinson's disease (PD). However, previous efforts used to tease out the role of nuclear aSyn in neurodegeneration have relied on overexpression, affecting its aggregation propensity, thereby clouding data interpretation. We engineered a mouse line in which endogenous aSyn is localized to the nucleus via a nuclear localization signal (NLS; Snca-NLS). We characterized these mice on a behavioral, histological, and biochemical level and recorded the progression of disease in mice from 2-19 months. The Snca-NLS mice exhibit age-dependent motor deficits and decreased survival rate. Histological analyses revealed motor cortex atrophy, specific to layers 5/6, in the absence of midbrain dopaminergic neurodegeneration. Additionally, the lack of aSyn phosphorylation or aggregation suggests that these phenotypes are not tied to what is typically thought as pathological aSyn. Rather, these results suggest that chronic endogenous nuclear aSyn can elicit a neomorphic toxic effect in mice in the absence of its aggregation. 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 disease. We are now exploring the molecular mechanism through which aSyn is toxic by generating its cellular compartment-specific interactomes via TurboID. By determining aSyn interacting partners within the nucleus, we can better understand its toxic function, ultimately shedding light on the role of nuclear aSyn in disease.

P2-C-356: Activity dependant condensation of the Fmr1 gene product in live cells

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Fragile X syndrome (FXS) is caused by a drastic downregulation of the Fmr1 gene product, the Fragile X messenger ribonucleoprotein 1 (FMRP). FMRP, we have recently discovered, participates in channel

activity modulation in its soluble form, whereas, the condensed form, holds the mRNA segregated from the translational machinery, thus inhibiting protein synthesis. However, this equilibrium between soluble and condensed and how this affects neuron activity remains ill defined. To study FMRP condensation assembly and disassembly in real time, we have generated an array of fluorescent vectors that form Förster Resonance Energy Transfer (FRET) pairs which can measure direct protein-protein interaction in live cells as measured by a reduction in fluorescence lifetime (FLIM microscopy). To ascertain FMRP-FMRP binding, we have produced fluorescently-tagged fragments that isolate the phase separation properties of FMRP. More specifically, the N-terminus of FMRP, which can bind to potassium channels, does not condense. The C-terminal participates in the dynamic transition between soluble and condensed pools as previously published. We are able to further isolate the binding partners of distinct sub domains of FMRP to important scaffolding and effector proteins, in rank order, based on their occupancy as measured by efficiency of FRET coupling. This study helps us understands the pleiotropic roles of FMRP and the biology of phase separation.

P2-C-357: Post-mortem analysis of Parkinson's disease brains after long-term deep brain stimulation of the subthalamic nucleus

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective surgical treatment for Parkinson's disease (PD), alleviating motor symptoms and restoring patients' quality of life. However, research into the long term effects of DBS on the human brain is lacking. This study aims to investigate the neuroanatomical and neurochemical alterations induced by chronic stimulations of the STN, and to correlate these changes with clinical outcomes and estimated electrical current delivered in the brain parenchyma. Brains of PD patients who had received more than 9 years of DBS treatment in the STN were used. For each brain, 3D graphical representations of the basal ganglia (BG) and DBS electrode were produced to determine the electrical current propagation using a patient-specific computational model (StimVision2). Immunofluorescence and confocal microscopy were used to determine the immunoreactivity of various proteins within the basal ganglia. Stereological quantification and morphological analyses of different cell types and blood vessels were performed. Near active contacts, elevated levels of GLUT1 were observed, indicating increased blood vessel growth. Additionally, IBA1+ microglia count was unchanged while CD68 expression was reduced suggesting no inflammatory response. However, detailed morphological analysis of microglia indicates a more active state near the stimulated area of the STN. Our post-mortem analysis indicates changes induced by long-term DBS of the STN involving glial cells and blood vessels, which do not appear to be detrimental to the patient.

P2-C-359: Metabolic syndrome induced by hypercalonric diets and hyperlipidic diets differ with respect to neuroinflammation

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Introduction: High fat diets and high carbohydrate diets can induce metabolic syndrome, a public health issue worldwide that increases the risk of cardiovascular and neuroinflammatory-induced neurodegenerative diseases. The difference between these diets on neuroinflammation is poorly understood as both lead to it; however, given the different structure and chemical nature of lipids and carbohydrates, as well as their known participation in different metabolic pathways, it is to be expected that they also respond physiologically in a different way to an exacerbated consumption of these biomolecules. Methods: To address this, we measured inflammatory markers in rats with metabolic syndrome induced by placing them on either a high fat or a high carbohydrate diet for 3 months. Results: We found that both diets induced metabolic syndrome as measured by the concentration of lactate, glutamate, fatty acids and the activities of Aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. In the brain, the high fat diet and the high carbohydrate diet had different effects on TNF-α, IL-1β, and IL-6 expression, classic inflammatory markers. Additionally, the high fat diet resulted in an increase in fatty acid levels and CD36 expression in the hippocampus and frontal cortex. Discussion: These results demonstrate that metabolic syndrome induced by a hypercaloric diet differs from that induced by a hyperlipidic diet, particularly with respect to neuroinflammation. It is important to establish these differences and understand the molecular mechanisms involved to address possible viable solutions to common diseases among the population that can be derived from their diet.

P2-C-360: Synaptic modulation of glutamate and dopamine release in striatum of the YAC128 mouse model of Huntington disease

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Studies have suggested that an imbalance between direct and indirect pathway activity contributes to early motor symptoms in Huntington disease (HD). Degeneration of striatal D2-expressing indirect pathway medium spiny neurons (iMSNs) precedes that of D1-expressing direct pathway ones (dMSNs), promoting involuntary movements. However, altered corticostriatal synaptic function precedes degeneration. In addition to iMSNs, D2 receptors are expressed on striatal dopaminergic inputs from substantia nigra, glutamatergic cortical inputs, and striatal cholinergic interneurons. D2-mediated signaling on iMSNs also promotes endocannabinoid (eCB) synthesis and consequent inhibition of glutamate release. Altered dopaminergic, eCB and cholinergic signaling may contribute to early striatal dysfunction in HD. We used optogenetic probes iGluSnFR and dLight to monitor glutamate and dopamine release in acute brain slices of YAC128 HD mice and wild-type (WT) controls. 0.5uM and 5uM of the D2 agonist quinpirole reduced cortically-evoked glutamate release in striatum of YAC128 slices, whereas only 5uM quinpirole reduced glutamate release in WT. We are testing whether increased D2 sensitivity in HD mice is due to: 1) increased D2 expression on cortical terminals; 2) reduced D2 signaling on dopamine terminals; 3) amplified eCB release from D2 activation on MSNs; or 4) upregulated D2 signaling on cholinergic interneurons. Our results show no genotype difference in cortically-evoked

dopamine release in striatum, and we are testing the other possibilities using pharmacological and immunostaining approaches. Our findings will provide a greater understanding of the interplay between key neuromodulators that regulate glutamate transmission and potentially give rise to motor symptoms in HD.

P2-C-361: Investigation of the role of Parkin in the context of idiopathic Parkinson's Disease and ageing using induced neurons

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Age-associated impairments such as oxidative stress and protein aggregation are involved in PD (Parkinson's Disease) pathophysiology. However, it is unclear what the exact mechanisms involved in these alterations are. Unlike in monogenic forms of PD, the contribution of the PINK1/Parkin pathway to idiopathic forms remains unknown. Here, we aim to better understand the role of Parkin in the context of idiopathic PD and ageing in directly converted dopaminergic neurons (iDANs) derived from patients' fibroblasts. To this end, we are using direct neuronal conversion from human dermal fibroblasts, which preserves the age signature of our different cell lines, from idiopathic and familial PD patients, as well as age and sex-matched controls. We submitted iNs to an oxidative stress agent Antimycin A or H2O2 and we measured the expression of different oxidative stress markers. Our preliminary data shows a significant increase in Parkin expression following direct reprogramming of fibroblasts into iNs. Furthermore, iNs exposed to antimycin A exhibit an increase of superoxide anion production. While iDANs from healthy donors exert a significant increase in lipid peroxidation following antimycin A challenge, iNs from PD patients did not show such increase. Experiments are ongoing to decipher this and whether it relates to changes in Parkin expression. Our preliminary results support the relevance of our model to study age-associated changes in Parkin and its role in idiopathic PD and how it could be linked to different aspects of PD pathophysiology leading to dopaminergic neurodegeneration.

P2-C-362: Pomalidomide improves motor behavioral deficits and protects cerebral cortex and striatum against neurodegeneration through a reduction of oxidative / nitrosative damages and neuroinflammation after traumatic brain injury

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Neuronal damage resulting from traumatic brain injury (TBI) causes disruption of neuronal projections and neurotransmission that contribute to behavioral deficits. Cellular generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is an early event following TBI. ROS often damage DNA, lipids, proteins and carbohydrates while RNS attack proteins. The products of lipid peroxidation 4-hydroxynonenal (4-HNE) and protein nitration 3-nitrotyrosine (3-NT) are often used as indicators of oxidative and nitrosative damages. Pomalidomide (Pom) is an FDA-approved immunomodulatory drug clinically used in treating multiple myeloma. Here we further compared the effects of Pom in cortical and striatal tissue focusing on neurodegeneration, oxidative and nitrosative damages, as well as

neuroinflammation following TBI. Sprague-Dawley rats subjected to a controlled cortical impact were used as the animal model of TBI. Systemic administration of Pom (0.5 mg/kg, i.v.) at 5 h post-injury alleviated motor behavioral deficits, contusion volume at 24 h after TBI. Pom alleviated TBI-induced neurodegeneration stained by Fluoro-Jade C in both cerebral cortex and striatum. Notably, Pom treatment reduces oxidative and nitrosative damages in cortical and striatal tissues of TBI rats and is more efficacious in stratum (93 % reduction in 4-HNE- and 84 % reduction in 3-NT- positive neurons) than in cerebral cortex (42 % reduction in 4-HNE- and 55 % reduction in 3-NT- positive neurons). Additionally, Pom attenuated microgliosis, astrogliosis and elevations of proinflammatory cytokines in cortical and striatal tissue. We conclude that Pom may contribute to improved motor behavioral outcomes after TBI through targeting oxidative/nitrosative damages and neuroinflammation.

P2-C-363: Characterizing neurodevelopmental impairments using 15q13.3 microdeletion patient-derived 3D brain organoids

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The 15q13.3 microdeletion syndrome is a common genetic disorder associated with multiple neurodevelopmental disorders such as autism spectrum disorder, schizophrenia, and epilepsy. Our previous studies highlighted that postnatal cortical excitatory neurons are a vulnerable cell type in this disorder; however, this late-stage screening leaves a considerable gap in our understanding of what may precede the postnatal developmental impairments. We are using unguided (cerebral) and region-specific forebrain organoids derived from 15q13.3 deletion patients to identify critical windows and vulnerable brain regions throughout prenatal development that may precede these postnatal impairments. Using bulk and scRNA sequencing at multiple timepoints, we are capable of profiling the developmental trajectory of this disorder, and have identified early growth abnormalities, maturation impairments in newborn neurons, as well as global disruptions in cell-cell signaling. To understand the effects of perturbed maturation on neural circuitry, we generated sparsely labeled dorsal-ventral forebrain assembloids and found impaired migration of ventral inhibitory neurons. Lastly, we are combining this approach with spatial and scRNA sequencing to identify affected cell types and cytoarchitectural changes within the 15q13.3 assembloid system. In summary, we hope that our combination of cell type characterization, pathway identification, and circuitry phenotyping will provide a thorough understanding of how the 15q13.3 deletions impairs prenatal development in multiple 3D neural models.

P2-C-364: Characterizing a novel substance for the treatment of hereditary spastic paraplegia type 4 using induced pluripotent stem cell-derived neurons

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Hereditary spastic paraplegia (HSP) defines a genetically and clinically heterogeneous group of monogenic neurodegenerative disorders. Clinical features comprise spasticity of the lower limbs,

frequently accompanied by weakness. Mutations in SPAST, coding for the protein spastin, are the most frequent cause of HSP. Spastin is known to act as a microtubule (MT) severing protein with implications in diverse cellular processes. Patients with pathogenic spastin variants express less spastin, which results in less severing of MTs. No unifying pathological mechanism explains the detrimental axonopathy observed in patients, however, dysfunctions of various cellular mechanisms have been implicated in SPAST-HSP including MT stability directly affecting axonal transport of organelles. To date, no causative therapy is available for the treatment of SPAST-HSP. In search of a novel compound, we identified a substance that had previously shown neuroprotective qualities in other neurodegenerative diseases, potentially via its interaction with MTs. To further characterize the effect of the substance, we used induced pluripotent stem cell (iPSC)-derived neurons derived from SPAST-HSP patients, and isogenic control lines. We show that the substance rescues store-operated calcium entry, a process we previously described to be reduced in SPAST-HSP iPSC-derived neurons, and the axonal transport of mitochondria, which is also known to be diminished in SPAST-HSP. Future studies in Danio rerio and Drosophila melanogaster shall reveal the functional effect of the substance on living SPAST-HSP models.

P2-C-365: Nitrative stress differentially affects proNGF retrograde axonal transport via each of its receptors in aged basal forebrain cholinergic neurons

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Retrograde axonal transport of proNGF is critical for survival of basal forebrain cholinergic neurons (BFCNs). ProNGF binds two receptors, TrkA and p75. TrkA, but not p75, decreases with aging. Aging impairs retrograde transport of proNGF and also increases nitrative stress. However, it is unknown if aging differentially affects TrkA- and p75-mediated proNGF transport. Addressing these unknowns is critical, as proNGF transport deficits correlate with cognitive decline, and the biological activity of proNGF depends on its receptors. We investigated whether aging and nitrative stress differentially affect proNGF transport via TrkA vs. p75 and whether this impacts cell signaling. Rat BFCNs were cultured in microfluidic chambers and aged for 7-21 days. ProNGF mutants that selectively bind to either TrkA (proNGF-KKE) or p75 (proNGF-Δ9-13) were quantum dot-labelled and added to BFCN axons. Axonal transport and somal signaling were analyzed via live imaging and immunocytochemistry, respectively. In vitro aging increased nitrative stress and transport of proNGF-Δ9-13 but decreased transport of proNGF-KKE. L-NAME treatment decreased nitrative stress, increased transport of proNGF-KKE, and decreased transport of proNGF-Δ9-13 in aged BFCNs. ProNGF-Δ9-13 increased apoptotic signaling and decreased survival signaling, whereas proNGF-KKE increased survival signaling. These results indicate that age-induced nitrative stress decreases transport of proNGF via TrkA while enhancing p75-mediated proNGF transport, resulting in increased apoptotic signaling and decreased neurotrophic signaling.

P2-C-366: Vascular and blood-brain barrier-related changes underlie stress responses and resilience in female mice and depression in human tissue

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Major depressive disorder (MDD) is the leading cause of disability worldwide and women have a roughly twofold higher risk than men. Only 30% of patients completely remit from MDD, suggesting that neuron-centric traditional treatments do not address important causal biological factors. Clinical studies report higher prevalence of MDD in patients suffering from cardiovascular diseases or stroke, indicating that increased inflammation and vascular dysfunction may contribute to depression pathogenesis. However, the vast majority of MDD studies have been conducted exclusively in males, leading to causal biological factors being omitted. Recent evidence shows that chronic social stress in male mice induces blood-brain barrier (BBB) leakiness in the nucleus accumbens, a critical structure for stress response. This promotes infiltration of harmful peripheral immune signals into the brain leading to establishment of depressive behaviors. These effects have not been studied in female mice. I hypothesize that MDD leads to sex-specific neurovascular adaptations, which may explain heightened vulnerability in women and sex-symptomatology observed in depressed patients. Therefore, I investigated BBB function under a 10-day chronic social defeat stress paradigm, a mouse model of depression mimicking human bullying. Comparison of stress-induced transcriptional pattern of key BBB genes revealed region-specific adaptations in the BBB of stressed males vs females and human post-mortem tissue. Additionally, blood profile correlated with behavioral and transcriptional findings unraveled promising BBB-related biomarkers of depression and resilience. It is imperative to consider sex-differences as a variable to develop innovative and adapted therapeutic strategies for MDD treatment.

P2-C-367: Administering ketamine to Rickrolled mice lacking vesicular zinc

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Major depressive disorder (MDD) is a highly prevalent neuropsychiatric disorder that is commonly treated with monoamine-targeting antidepressants. Unfortunately, one third of patients with MDD do not respond to these therapies. Recently, the use of ketamine, an N-methyl-D-aspartate receptor (NMDAR) antagonist, has emerged as a promising treatment for MDD, displaying rapid and sustained antidepressant effects. However, its effects when combined with zinc remain unclear. Patients with MDD have reduced levels of zinc, and zinc supplements as an adjunctive therapy have been shown to improve depressive symptoms, potentially through its actions as a neurotransmitter. Similar to ketamine, zinc acts antagonistically on NMDARs. This phenomenon is facilitated by zinc transporter 3 (ZnT3), which sequesters zinc into synaptic vesicles. Using a ZnT3 knockout (KO) mouse model that lacks vesicular zinc, we investigated the interplay between vesicular zinc and ketamine in stress. Wildtype (WT) and ZnT3 KO mice were subjected to multiple simultaneous acute stress (MAS) or standard housing conditions for 10 days. Mice were subsequently administered ketamine (10 mg/kg) or saline, followed by a battery of behavioural assays before their brains were stained using the Golgi-Cox staining method. Behavioural analyses revealed that MAS and ketamine induced changes in depressive- and anxiety-like behaviours, in

a genotype- and sex-dependent manner. We also show that depending on genotype and sex, ketamine differentially altered the length and number of dendritic arborizations in the prefrontal cortex. Together, these findings support the combined role of vesicular zinc and ketamine in modulating depressive phenotype.

P2-C-368: A multi-omics approach to the identification of biological signatures in Parkinson's disease and atypical parkinsonisms

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Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. There is considerable heterogeneity in the clinical presentation of parkinsonian syndromes, including typical PD and atypical parkinsonism (AP). Currently, the pathophysiology of these disorders is not well understood, and there are no biomarkers for positive or differential diagnosis of PD and AP. As a result, patients may be misdiagnosed and may not receive appropriate treatment. We are using a multi-omics approach combining genomics, transcriptomics, epigenetics and proteomics to identify biomarkers in these parkinsonian disorders. Our study population consists of patients with PD, AP (Multiple System Atrophy - MSA, Progressive Supranuclear Palsy - PSP) and healthy controls. Our analyses will be performed on peripheral blood mononuclear cells. Our first study cohort of 09 PD patients, 02 MSA patients and 01 PSP patient whose DNA we sequenced allowed us to find variants likely to have an impact on the transcriptomic and proteomic level, as well as on the DNA methylation profile, which we will soon confirm. Our results could partially elucidate the mechanisms of PD and AP, but also identify a potential biomarker to help diagnose this disease, even in the pre-symptomatic stage. In addition, the results of this study will add value to the search for new therapies by providing a better understanding of the pathophysiology of PD and AP.

P2-C-369: Region-specific astrocyte alterations underlie chronic stress response in male mice

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Major depressive disorder (MDD) is a severe neuropsychiatric illness. Alterations of the blood-brain barrier (BBB), formed by endothelial cells, pericytes and astrocytes, are observed in individuals with MDD and after exposure to chronic social defeat stress (CSDS), a mouse model of depression. Astrocytic morphological changes such as reduced end-feet coverage of blood vessels, occur in the MDD brain and are associated with inflammation and impaired function of these glial cells. However, possible contributions to MDD pathogenesis and maladaptive stress responses remain to be determined. Male mice were subjected to 10-day CSDS producing two subpopulations: stress-susceptible (SS) animals which are characterized by depression-like behaviors and resilient (RES) mice behaving like unstressed controls. CSDS induces BBB hyperpermeability in a region-specific manner, leading to infiltration of

inflammatory mediators and development of depressive-like behaviors in SS but not RES animals. Reduced gene expression of connexin gap-junctions, linking neuronal and vascular activity, was noted in the nucleus accumbens of SS male mice, a hub for reward and mood regulation. Conversely, increased expression of growth factors was observed in the prefrontal cortex of RES animals, suggesting compensatory mechanisms in this brain region, important for decision-making and social behaviors. Functional measurements are ongoing to better define the role of astrocytes in the development of depression-like vs proper stress-coping behaviors. Together, these results suggest that astrocytes could actively contribute to susceptibility vs resilience to chronic stress exposure, and possibly MDD, in a brain region-specific manner.

P2-C-370: Pdgfra-dependent Polr3b exon loss recapitulates POLR3-related hypomyelinating leukodystrophy phenotypes in vivo

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POLR3-HLD is a devastating neurological disease characterized by severe diffuse hypomyelination and progressive functional decline leading to early death. It is caused by biallelic pathogenic variants in genes encoding Pol III subunits. We hypothesize that mutations in Pol III subunits such as POLR3B reduce enzyme function during a critical developmental period causing defective myelinogenesis and hypomyelination. We characterized the impact of a POLR3B mutant lacking exon 10 (POLR3BΔ10) on Pol III complex assembly, nuclear import, and protein expression in human cells. We developed an inducible/conditional animal model using the cre/lox system to express the orthologous mutation in a Pdgfrα-dependent manner during postnatal development in mice. The animal model was characterized using a variety of techniques including tissue biochemistry, histology, and advanced imaging (microCT, ex vivo MRI). POLR3BΔ10 expression was shown to cause a severe Pol III assembly defect accompanied by reduced expression and nuclear import of the mutant protein in human cells. Inducing Pdgfrα-dependent expression of orthologous Polr3bΔ10 during postnatal development in mice causes severe hypomyelination, craniofacial defects, and hypodontia. The hypomyelination phenotype was caused by proliferation and maturation defects in oligodendrocyte-lineage cells carrying homozygous Polr3bΔ10, which preceded hypomyelination and led to non-apoptotic cell loss from the brain parenchyma. We describe the first severe model of POLR3-HLD and the first working disease model based on mutation of Polr3b. This work advances our understanding of POLR3-HLD and implicates defective proliferation and differentiation of oligodendrocyte-lineage cells as key features of POLR3-HLD pathogenesis.

P2-C-371: Altered movement-related spontaneous and sensory-evoked cortical activity in vivo in huntington disease model-mice

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Huntington disease (HD) is a fatal, age-related, monogenic inherited neurodegenerative disorder, characterized by progressively disordered cognition and movement, due largely to profound striatal and cortical neuron dysfunction and subsequent degeneration. Although cortical-circuit dysfunction likely underlies much of the cognitive impairments seen in HD and contributes to striatal degeneration, cortical circuits are relatively understudied in HD models. Our group recently showed that equivalent sensory input, from various modalities (sight, sound, touch), activates greater cortical surface area in lightly anaesthetized HD-model-mice (sensory-spread). Here we've used zQ175 HD-mice, which selectively express GCaMP6 in cortical pyramidal neurons, to repeatedly examine mesoscale cortical activity in awake-behaving animals, across multiple disease stages. We report that acute visual stimulation elicits significantly greater sensory-spread in awake-behaving 6 - 8-month-old HD-mice, as was the case in anaesthetized animals. However, in contrast to sensory-spread, HD-mice showed reduced amplitudes of spontaneous movement-related cortical events. At premanifest 3 - 5 months-age, sensory responses were not different between HD and wildtype (WT) mice; however, amplitudes of spontaneous cortical events were still reduced relative to WT, indicating this is the more developmentally proximal effect. We hypothesize increased cortical sensory responses reflect compensatory circuit changes in response to reduced cortical activity in HD-mice and are exploring underlying mechanisms with further in vivo imaging and brain slice electrophysiology. Support: JM: Hereditary Disease Foundation (HDF), YW: Vanier Award.

P2-C-372: Examining neurovascular dysfunction in depressed suicides with a history of childhood abuse

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Introduction: Childhood abuse is experienced globally by approximately 1 billion youth aged between 2-17 years (Hillis et al., 2016). Abnormal blood vessel morphology, downregulation of tight junction protein claudin5 (Cldn5) and altered epigenetic regulation of Cldn5 have been reported in the nucleus accumbens of mice exposed to chronic stress (Menard et al., 2017; Dudek et al., 2020). However, the impact childhood abuse has on cerebrovascular integrity has yet to be investigated in humans. Hypothesis: We hypothesize that a history of early-life stress exacerbates the alterations in cerebrovasculature suggested by previous studies of chronic stress experienced in adulthood. Methods: Well-characterized frozen postmortem ventromedial prefrontal cortex (vmPFC) samples from adult male and female depressed suicides with a history of severe childhood abuse and matched sudden-death controls (n=25/group) were obtained from the Douglas-Bell Canada Brain Bank. To test this hypothesis, we developed a protocol to enrich and isolate microvessels using mechanical homogenization and centrifugation-separation, from which total RNA was extracted for library preparation and RNA-sequencing on the NovaSeq6000 system (Genome Quebec). Results: Differential gene expression

analysis reveals that abused suicide subjects exhibit increased expression of transmembrane transporters and steroid receptors; as well as suppression of MHC protein complex-related genes. These results suggest that childhood abuse leads to latent dysfunction in several molecular functions at the neurovascular unit in adulthood.

P2-C-373: Numb regulates Tau levels and prevents neurodegeneration in tauopathy mouse models

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Accumulation of the microtubule-associated protein Tau is linked to neuronal cell death in tauopathies, but how intraneuronal Tau levels are regulated in health and disease remains unclear. Here, we show that conditional inactivation of the trafficking adaptor protein Numb in retinal ganglion cells (RGCs) increases Tau levels and leads to axonal blebbing, which is followed by neuronal cell loss in aged mice. In the TauP301S mouse model of tauopathy, conditional inactivation of Numb in RGCs and spinal motoneurons accelerates neurodegeneration, and loss of Numb in motoneurons also leads to precocious hindlimb paralysis. Conversely, overexpression of the long isoform of Numb (Numb-72) decreases intracellular Tau levels and reduces axonal blebbing in TauP301S RGCs, leading to improved electrical activity in cultured neurons and improved performance in a visually guided behavior test in vivo. These results uncover Numb as a key regulator of intracellular Tau levels and identify Numb-72 as a potential therapeutic factor for tauopathies.

P2-C-374: CSF oligoclonal band frequency in a Cuban cohort of patients with multiple sclerosis. comparison with Latin American countries and association with latitude

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Background. The diagnostic sensitivity of CSF specific oligoclonal bands (OCBs) in multiple sclerosis (MS), using state of the art methods, has been clearly established to be over 95% in patients with a predominantly Caucasian background. This is not the case for other geographical regions. Objective. to assess the frequency of OCBs in a cohort of MS patients evaluated at the Institute of Neurology and Neurosurgery (Havana, Cuba), and to review the scientific literature in order to investigate the possible relationship between OCB status and latitude in the region of Latin America. Methods. Fifty-three patients (47 with definite MS and 6 with clinically isolated syndrome - CIS) were included. Isoelectric focusing with IgG immunoblotting for OCB analyses. PubMed, Scielo and Google Scholar were searched for papers containing information concerning CSF OCB status in patients with definite MS in Latin America and the Caribbean. Results. In Cuban patients with definite MS, an OCB prevalence of 87% was

observed while the frequency in CIS patients was lower (67%). The prevailing pattern was that of OCBs restricted to the CSF (type 2), which was observed in 71% of definite MS patients. OCB prevalence was slightly lower, but very close to that reported in Caucasian populations. Conclusions. A prevalence of CSF restricted OCBs was slightly lower, but similar to that reported in Caucasian populations. The analysis of OCB frequency in Latin American countries revealed a possible relationship between OCB prevalence and latitude, but this must be further investigated.

P2-C-375: Vascular contributions to neural precursor fate following postnatal inflammation

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INTRODUCTION: Acute systemic infection during childhood can lead to long-term neurological impairments. Interleukin-6 (IL-6) is a main contributor in this regard. Our lab previously showed that systemic IL-6 affects ventricular-subventricular zone (V-SVZ) neural stem cells (NSCs); however, the underlying cellular mechanisms remain to be elucidated. How does IL-6 affect the physical and secreted cues between NSCs and endothelial cells (ECs)? How does IL-6 affect mural cell contribution to the blood-brain barrier? We aimed to address these questions by investigating the role of the vasculature on postnatal NSC fate following systemic inflammation. METHODS: Utilizing single-cell transcriptomics, we studied the effects of systemic IL-6 on the murine postnatal V-SVZ. We assessed communication of V-SVZ ECs with NSCs using ligand-receptor modelling. We also began analysis of cleared brain tissue and assessed in vitro EC conditioned media effects on cortical precursor (CP) proliferation and differentiation. RESULTS: Our data indicates that postnatal systemic IL-6 exposure leads to a pro-inflammatory transcriptional phenotype in the V-SVZ microglia and perturbs EC signalling onto NSCs. Preliminary data suggests that in vivo IL-6 increases V-SVZ vascular permeability and in vitro IL-6 disrupts the positive effects of EC conditioned media on CP proliferation and differentiation. CONCLUSIONS: Our results indicate that postnatal systemic IL-6 induces a pro-inflammatory V-SVZ microenvironment and suggests that EC signalling plays an important role in determining neural precursor fate.

P2-C-376: Interplay between the endolysosomal system and protein aggregation in the pathogenesis of Parkinson's Disease

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Alpha-synuclein (aSyn) aggregation has been recently linked to endolysosomal dysfunction as one of the early events in Parkinson's disease (PD) pathogenesis. However, the precise sequence of events surrounding aSyn aggregation and its molecular interactions with the vesicles of the endolysosomal system (ELS), leading to neuronal death, remains elusive. To answer this question, we created a new optogenetic-based model of PD that allows for the real-time induction and monitoring of aSyn aggregation and Lewy bodies-like formation (LIPA system). Using this system, we investigated the interactions between aSyn inclusions and the ELS, by combining STED and transmission electron microscopy (TEM) overtime. Then, we used live-cell microscopy to decipher how aSyn interacts with the

ELS at the very first steps of aggregation process. These high-resolution techniques allowed us to capture, for the first time, the interaction of aSyn aggregates with the vesicles and how it affects their trafficking. Interestingly, aSyn shows very strong interaction with lysosomes. We were able to modulate this interaction by inducing key mutations at the interaction site. These results allowed us to observe and to better understand how is mediated aSyn aggregation in the context of PD, suggesting that the ELS play a key role in aSyn aggregation. Deciphering this complex interaction could pave the road to a better comprehension of the disease and lead to the discovery of new therapeutic strategies targeting the interaction between aSyn and the ELS.

P2-C-377: Huntington's disease: the impact of wild-type huntingtin reduction on nuclear morphology in primary hippocampal culture

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Huntington's Disease (HD) is a genetically inherited neurodegenerative disorder characterized by psychiatric, motor, and cognitive symptoms. HD is caused by a mutation in the huntingtin gene (HTT), producing the harmful mutant huntingtin (mHTT) protein. Wild-type huntingtin (wtHTT) is the 'healthy' protein variant and is ubiquitously expressed in neurotypical individuals. wtHTT is essential to numerous rudimentary cellular functions; it is vital for embryonic development, and acts as a scaffolding protein and transcriptional regulator. Some genetic therapies for HD involve targeting HTT at the RNA level, but many are non-selective, hence reducing both mHTT and wtHTT. The consequences of wtHTT reduction remain poorly understood. Here, we used siRNA to reduce wtHTT in primary hippocampal culture and Western blot methods were used to confirm its reduction. Preliminary results have shown that when wtHTT is lowered, there is a significant increase in nuclear size relative to the soma. To further investigate this, we are assessing the consequences of wtHTT depletion on nuclear chromatin morphology through analysis of methyl-CpG-binding-protein 2 (MeCP2) distribution. MeCP2 has been shown to regulate chromatin structure and interacts directly with wtHTT. We are now combining ICC with super-resolution microscopy methods to determine 3D morphology of heterochromatin as well as MeCP2 intensity levels. We hypothesize that wtHTT regulates MeCP2 protein levels, based on their interaction, and wtHTT loss will therefore alter nuclear size. It is important to study the impact of reduced wtHTT on the brain to weigh the consequences of its reduction in potential therapies and in the progression of HD.

P2-C-378: Distinct injury response of human oligodendrocytes to metabolic stress: relevance for progressive multiple sclerosis

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Oligodendrocyte (OL) loss is a central feature of progressive MS. A potential cause for this loss is metabolic stress. Here we aim to define the injury response of primary human OLs (hOLs) to metabolic stress (reduced glucose/nutrients) in vitro and relate these to OLs in cases of MS. In MS lesions and in vitro under stress conditions, we observe cell shrinkage and a reduction in OL nuclear area. Under metabolic stress, we detect reduction in ATP per cell that precedes changes in survival. Autophagy was initially activated, although ATP levels were not altered by autophagy modulators. Prolonged stress resulted in autophagy failure. Although prolonged stress resulted in increased ROS and cleavage of spectrin, cell death was not prevented by inhibitors of ferroptosis or MPT-driven necrosis, the regulated cell death (RCD) pathways most likely to be activated by metabolic stress. hOLs had decreased expression of VDAC1, VDAC2, and genes regulating iron accumulation and cyclophilin. Consistent with in vitro results, we detected an increase in autophagosomes in OLs in MS lesions compared to controls. Gene expression analysis indicated lack of up-regulation of RCD pathways in OLs in active MS lesions. We conclude that this distinct response of hOLs, including resistance to RCD, reflects the combined impact of autophagy failure, increased ROS, and calcium influx, resulting in metabolic collapse and degeneration of cellular structural integrity. Defining the bases of OL injury and death in MS provides guidance for development of protective strategies.

P2-C-379: Effects of altering neural heterogeneity and myelination patterns on epileptiform activity

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An estimated 50 million people are affected by epilepsy worldwide, and due to insufficient understanding of its pathology, current treatments are only partially effective. Neural heterogeneity is a strong protective factor against epilepsy. Similar to how biodiversity protects against spread of infectious disease, diversity in neuron populations protects against propagation of seizures. Heterogeneity of excitatory and inhibitory populations are investigated for their role in the over synchronous seizure activity. This is done with computational mean field modeling based on Wilson-Cowan equations. While both populations alter epileptiform activity, we see inhibitory neurons having a greater effect in synchrony suppression, possibly due to their direct counteraction of hyperactivity through inhibition. Where greater inhibitory diversity reduces interictal spiking drastically relative to its excitatory counterpart. Recently, maladaptive myelination caused by seizures has been shown to increase epilepsy progression. Investigating effects of irregular myelination associated with seizure activity is thus an important avenue to explore. Myelination patterns can be studied by altering delay times in the aforementioned Wilson-Cowan models. To examine effects of altering myelination and heterogeneity measures, we look to corresponding frequencies of oscillation in mean membrane potential, and the power spectrum. These two variables distinguish states of greater epileptiform activity, thus indicating parameters that can drive a system away from hypersynchrony, and towards stability.

P2-C-380: Studying neuropathogenic mechanisms of human mutants in the receptor tyrosine kinase EPHB2

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Abnormal neural circuit development often results in brain malformations. The corpus callosum is the most prominent connection in the human brain, linking the left and right cerebral hemispheres, with its size correlated with the degree of brain evolution. Agenesis of the corpus callosum (ACC) is a common brain malformation that can occur either in isolation or with congenital syndromes such as autism spectrum disorder (ASD). ACC patients frequently show deficits in higher-order cognition and social skills, reflecting the importance of interhemispheric communication in highly evolved brains. In the nervous system, the EPH family members of receptor tyrosine kinases propagate contact-mediated cell-cell signaling between neurons, promoting cell repulsion or adhesion, which underlie neural circuit wiring. Interestingly, mice lacking EphB2, one of the Eph receptors, develop ACC and deficits in social behaviors, suggesting that the loss of EPHB2 may also cause similar phenotypes in humans. However, the EPHB2 requirement in the developing human nervous system is unknown. Moreover, the precise function of EPHB2 in corpus callosum formation remains elusive. Our team assembled a cohort of patients with mutations in the coding sequence of the EPHB2 human gene. All patients commonly show defects in corpus callosum development. Our biochemical and cellular assays show that each mutation perturbs different aspects of EphB2 signaling. Consistently, structure analysis suggests that EPHB2 mutations disrupt the proper folding of the receptor. Finally, we show that EPHB2 mutations modify neuronal response upon ephrin-EphB2 signaling. Together, our data provide the first insights into the role of EphB2 forward signaling in the development of the human nervous system.

P2-C-381: Ketogenic dietary challenges improve cognition and reveal liver-associated systemic abnormalities in AD mice

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Metabolic abnormalities involving both glucose and lipids are key features of Alzheimer's disease (AD). Since ketones are an alternative to glucose and lipids for cellular energy, we investigated the impact of dietary ketogenic interventions on the cognitive and metabolic responses of AD mice. Young adult 3xTg-AD and 5xFAD mice with their respective control mice were administered either a standard carbohydrate-rich diet (SD, 70% carbohydrate, 20% fat, 10% protein), an identical diet except that a portion of the fats were replaced with ketogenic medium-chain triglycerides (kMCT), or an extreme

carbohydrate-free ketogenic diet (KD). Notably, after 1 month on these diets, mice on both the kMCT and KD interventions showed improved performance in the Morris Water Maze test of hippocampus-dependent spatial learning and memory. Transcriptomic analysis of the hippocampus showed that kMCT and KD respectively restored 41% and 56% of genes altered in 3xTg-AD mice, including genes involved in synapses, myelin sheath and neurogenesis. To address the longer-term metabolic effects of these interventions, mice exposed to these diets for 6 months were evaluated using a variety of longitudinal measures of peripheral energy metabolism. Unexpectedly, 3xTg-AD mice on the KD (but not their controls) developed a dysregulation in peripheral lipid metabolism and hepatic transcriptomic changes. In contrast, 3xTg-AD mice on the kMCT diet showed evidence of improved peripheral energy metabolism. These data highlight the development of peripheral metabolism disturbances in AD mice and underscore the importance of clarifying the physiological mechanisms of ketogenic interventions to fully harness their therapeutic potential.

P2-C-382: Loss of C9orf72 perturbs the Ran-GTPase gradient and nucleocytoplasmic transport, generating compositionally diverse Importin β-1 granules in vivo

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A hexanucleotide (GGGGCC) repeat expansion in C9orf72 causes amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) eliciting toxic effects through generation of RNA foci, dipeptide repeat proteins and/or loss of C9orf72 protein. Defects in nucleocytoplasmic transport (NCT) have been implicated as a pathogenic mechanism underlying repeat expansion toxicity. Here, we show that loss of C9orf72 disrupts the Ran-GTPase gradient and NCT in vitro and in vivo. NCT disruption in vivo is enhanced by the presence of compositionally different types of cytoplasmic Importin β-1 granules that exhibit neuronal subtype-specific properties. We show that the abundance of Importin β-1 granules is increased in the context of C9orf72 deficiency, disrupting interactions with nuclear pore complex proteins. These granules appear to associate with the nuclear envelope and are co-immunoreactive for G3BP1 and K63-ubiquitin. These findings link loss of C9orf72 protein to gain-of-function mechanisms and defects in NCT.

P2-C-383: Physiological significance of increased VGluT2 expression by surviving mesencephalic dopamine neurons in mouse models of Parkinson?s disease.

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Dopamine (DA) neurons of the ventral midbrain are vulnerable to mitochondrial dysfunction and associated oxidative stress, and to protein aggregation. Recent in vitro and in vivo studies have revealed that DA neurons expressing the type 2 vesicular glutamate transporter (VGluT2), such as those found in the ventral tegmental area (VTA), are more resilient to PD pathogenesis. We have previously shown that modest levels of VGluT2 overexpression can promote the axonal connectivity of DA neurons and others

showed that strong overexpression can lead to neurotoxicity. Here we test if increased VGluT2 expression in surviving DA neurons in mouse PD models is accompanied by increased glutamate release at some of their axon terminals in the striatum. We are presently using RNAscope to quantify VGluT2 mRNA levels in surviving SNc and VTA DA neurons in the unilateral intra-striatal 6-OHDA mouse model and in the viral α-synuclein overexpression mouse model. To test our main hypothesis, we are also presently evaluating whether changes in VGluT2 levels cause functional changes in the propensity of DA neuron release sites to release glutamate. Our initial results reveal that we can detect optogenetically evoked glutamate-mediated EPSCs in both dorsal and ventral striatal medium spiny neurons in acute sections prepared from control and PD model mice. Preliminary results suggest increased glutamate release in α-synuclein overexpressing mice at 30 days post infection, an effect that is lost after six months, thus indicating that increased glutamate release is likely a transient feature.

P2-C-384: Olfactory bulb peptide profiling in depressed suicides reveals dysregulated astrocytic function

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Brain areas implicated in olfaction, including the olfactory bulb (OB), have been involved in the etiology of major depression mainly on the basis of rodent studies (e.g. bulbectomized rats). To explore the molecular features of the OB in major depression, global proteome analysis was carried out on 21 fresh-frozen human OB samples obtained from Douglas-Bell Canada Brain Bank from 11 depressed suicides and 10 age- and sex-matched controls. Our preliminary analysis indicates that 3712 proteins were detected in at least 50% of the samples from both cases and controls. Interestingly cell type-specific analysis uncovered a significant reduction in astrocytic proteins such as GFAP, ALDH1L1, ALDOC, GJA1 and SLC1A3 in depressed suicides compared to controls. This observation is consistent with our previous investigations showing a downregulation of canonical astrocytic markers in other brain regions in depressed suicides. To determine whether depression-associated OB astrocytic abnormalities are specific to humans, we also performed proteomics on the OB of socially defeated mice. Cell type specific analysis revealed that in this model of depression, the OB displays alterations in oligodendrocytic - but not astrocytic - profiles compared to controls, thus highlighting important species differences between samples from depressed patients and from an animal model of depression. Overall, these findings further highlight cerebral astrocytic abnormalities as a consistent feature in depression and suicide.

P2-C-385: NEDD4, a caspase substrate, is cleaved during serum starvation and fragments observed in the aging olfactory bulb

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Caspases are mediators of programmed cell death pathways and implicated in various physiological processes. Using a bioinformatics approach, proteins identified in a caspase-6 Y2H screen and known

caspase-6 substrates were filtered to highlight potential substrates that play an early role in apoptosis. The shortlisted candidates included NEDD4. This protein is a E3 ubiquitin-protein ligase and contains an N-terminal calcium and phospholipid binding C2 domain followed by multiple tryptophan-rich WW domains and, a C-terminal HECT ubiquitin ligase catalytic domain. It has been shown to play a critical role in cancer, epileptogenesis and in neurodegenerative diseases. We confirm cleavage of NEDD4 by caspase-3, -6 and -7, and show that the full-length form of NEDD4 is decreased following serum starvation in a striatal cell line. We also assessed the expression of NEDD4 in aging murine tissue and show that in the aging cortex and striatum no changes were observed compared to young murine tissue. However, in the olfactory bulb increased full-length and a 45kDa fragment of NEDD4 was detected with aging. Previous work has shown that with stress (Fas-mediated and ectoposide) there is an increase in the generation of NEDD4 fragments, caspase activation and cell death. Our results suggest that the NEDD4 protein may also implicated in the cell death induced by serum startavation, and may play a role in the atrophy of the aging olfactory bulb.

P2-C-387: Shedding light on Parkinsons disease GWAS genes

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Over the past two decades, the discovery of dozens of new Parkinson's Disease (PD) genes has provided a tremendous opportunity to better understand how PD develops. However, the discovery rate of new genes has far outpaced our progress in understanding their roles in PD. Indeed, the research community has focused on a few of the "popular" PD genes (SNCA, PKRN, LRRK2, GBA), while the rest remain understudied. We refer to this set of under-explored genes as the "PD Dark Genome". We feel that with the advent of new technologies such as genome editing and the ability to differentiate human stem cells into different types of brain cells, the time is ripe to start disentangling how these lesser-studied genes contribute to PD. Our goal is to characterize lesser-studied PD genes in human stem cell-derived differentiated brain cells by systematically investigating them 1) in cellular assays reflecting known PD pathways and 2) in discovery genomic assays to uncover new PD mechanisms. These assays will yield biological signature for each profiled gene and determine if they are indeed associated with PD, and if so, understand their role in PD pathogenesis. Using iPSC-derived DA neurons from the control cell line (AIW002-02) and 4 monogenic and PD risk gene KI/KOs (GBA KO, SNCA A53T, PINK1 KO and PRKN KO), we gathered a set of reference data, such as dopaminergic differentiation and maturation immunofluorescence profiling, alpha-synuclein accumulation, mitochondrial and lysosomal dysfunction, scRNAseq and TMT proteomics. These results will serve as an experimental toolkit and pipeline to 1) explore the biology of GWAS genes responsible for PD risk, and 2) elucidate their role in PD pathogenesis and how they contribute to known or novel PD pathways.

P2-C-388: The role of glutamate co-transmission by serotonin neurons of the dorsal raphe nucleus in L-Dopa-induced dyskinesia

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Parkinson's disease is mainly characterized by the progressive loss of midbrain dopaminergic neurons that innervate the striatum. The dopamine precursor L-3,4-dihydroxyphenylalanine (L-Dopa) is the most effective pharmacotherapy but its chronic use is hampered by side effects such as abnormal involuntary movements (AIMs), also termed L-Dopa-induced dyskinesia (LID). Studies have shown the crucial role of serotonin (5-HT) neurons in the conversion of exogenous L-Dopa and LID expression. Through this study, we specifically addressed the functional role of glutamate co-transmission by 5-HT neurons of the dorsal raphe nucleus (DRN) in the regulation of motor behavior and LID expression. We used CRIPSR-Cas9 technology and viral injections to knock-out or overexpress the atypical vesicular glutamate transporter 3 (VGluT3), specifically in the DRN 5-HT neurons of adult mice. Two weeks later, mice were injected with 6-OHDA in the medial forebrain bundle to selectively damage dopaminergic axons, and then treated with L-Dopa to induce AIMs. Post-mortem analysis confirmed the depletion or overexpression of VGluT3 in AAV-infected 5-HT neurons of the DRN as well as a severe dopamine denervation. After dopamine lesion and L-Dopa administration, VGluT3-depleted mice show exacerbated AIMs following the administration of a low dose of L-Dopa (1mg/kg), compared to controls and transgenic mice overexpressing VGluT3. At higher L-Dopa doses (3, 6, 12 mg/kg), mice overexpressing VGluT3 show higher severity of the orofacial AIMs subtype. Glutamate that is co-released by 5-HT neurons of the DRN appears to be involved in the expression of LID.

P2-C-389: Dysregulated intestinal neuro-immune axis underlying early Parkinson's disease symptoms

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Decades prior to clinical diagnosis, patients with Parkinson's disease (PD) often manifest non-motor symptoms, including constipation. Notably, intestinal inflammation and infection positively correlate with incidence of PD. Little is known nonetheless about the mechanisms at play during the evolution of disease originating in the gut. Our aim is to further characterize our previously established model, exhibiting late PD-like symptoms after repeated gut infection of mice deficient in PTEN-induced kinase 1 (Pink1 KO). We performed single cell transcriptomic analyses of colonic immune cells of Pink1 KO mice following acute bacterial infection as well as in vitro approaches to decipher inflammatory-mediated mechanisms of enteric neuron dysfunction. Our findings underscore that infected Pink1 KO mice display enhanced intestinal inflammation pointing to an aberrant myeloid cell lineage as drivers of early disease. The dysregulation in the innate immune response instigates a pro-inflammatory milieu conducive to enteric neuronal damage, which presumably underlies gut dysmotility observed in Pink1 KO mice following acute infection. Furrthermore, activated CD14+ monocytes isolated from blood of PD patients also reveal similarities in gene expression signatures promoting inflammation and interleukin-1 signaling

as with intestinal Pink1 KO monocytes after acute infection. The reduced PINK1 expression in activated CD14+ monocytes of PD patients may mimic a loss-of-function phenotype as seen with Pink1 KO mice. Collectively, we propose that Pink1 KO mice following acute intestinal bacterial infection constitute an optimal model to investigate neuroimmune-related dysregulation underpinning prodromal PD pathogenesis.

P2-C-390: Neuronal gene expression in multiple sclerosis and mouse model implicates a senescence-like phenotype

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Multiple sclerosis (MS) is a complex neuroimmune disease. Loss of brain volume, particularly of the grey matter, is one of the best clinical correlates to sustained disability for MS patients, suggesting that neurodegeneration in MS may be a relevant area of study to identify novel therapeutics. However, in order to identify neuroprotective drugs, it is imperative to understand how gene expression changes in neurons in response to inflammation. Methods: RNA-sequencing, miRNA-sequencing, and ATAC-sequencing techniques were performed on retinal ganglion cells from EAE mice at different timepoints. Additionally, previously published single-nucleus sequencing datasets from neurons from MS patients were reanalyzed to compare to findings in EAE. Immunohistochemistry (IHC) analyses were conducted to validate dysregulation of pathways of interest. Results: Pathway analysis of RNA-sequencing from EAE mice suggested a preponderance of senescence-associated pathways in neurons and correlated with transcriptomic changes seen in naïve aged mice. Single-nucleus sequencing of cortical neurons from grey matter of MS patients similarly confirmed the presence of a senescence like signature, characterized by alterations to cell cycle and DNA damage pathways. IHC confirmed that retinal ganglion cells in EAE mice accumulate yH2AX in their nuclei, and equally found changes in nuclear envelope proteins, cell cycle proteins and histone modifications.

P2-C-391: CRYAB contributes to termination of the pro-inflammatory macrophage response in injured aged peripheral nerves

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Regeneration of damaged, aged peripheral nervous system (PNS) neurons is poor. This is partly due to the reduced ability of some old PNS neurons to regrow. However, evidence indicates that non-neuronal cells in the environment of the aged PNS also participate. For instance, senescent Schwann cells display a reduced ability to differentiate into a repair phenotype after nerve damage while fewer blood-borne macrophages are recruited into damaged nerves. Further, the phagocytic ability of these aged cells is significantly reduced and as such, axonal and myelin debris that contain inhibitors against axon growth are not cleared thereby impeding axon regeneration. The molecular factors involved in the dysfunction of old Schwann cells and macrophages is still largely unknown. We investigated if CRYAB, a small heat shock protein that is expressed by Schwann cells and axons, impacts the presence of macrophages and Schwann cells in the injured, aged PNS. Following a sciatic nerve crush injury, 3 and 12 month old wildtype and CRYAB knockout sciatic nerves were immunohistochemically processed and analyzed for the number of Schwann cells, macrophages and myelin profiles. While CRYAB did not alter the number of Schwann cells in old injured sciatic nerves, more pro-inflammatory macrophages persisted in 12 month old null nerves after damage. Further, CRYAB null macrophages cells were more efficient in clearing myelin debris compared to controls. CRYAB thus plays a role in dampening pro-inflammatory macrophage responses and promoting myelin debris clearance after injury to the aged PNS.

P2-C-393: Nuclear lamina invagination, a reversible damage in an in-vitro model of tauopathy

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Human tauopathies are characterized by intracellular aggregation of hyperphosphorylated tau protein in neurons. Tau is involved in many cellular functions through its association with microtubules and actin filaments. In tauopathies overstabilization of filamentous actin (f-actin) leads to invagination of nuclear envelope. An intricate protein layer known as Nuclear Lamina (NL) is located at the interface of inner layers of nuclear envelope and chromatin. NL is degraded after nuclear envelope invagination, resulting in aberrant gene expression and re-emergence of ancient retroviruses. It is not clear if prevention of tau-hyperphosphorylation can prevent NL invagination and its downstream pathology. In this study, we first established that overexpression of full-length tau and the 35kDa C-terminal fragment (Tau35) in differentiated human neuroblastoma (dSH-SY5Y) cell lines enhanced tau hyperphosphorylation and nuclear lamina invagination; however, these changes were significantly exacerbated in Tau35-overexpressing cells. Application of two small molecule inhibitors of c-Jun N-terminal kinase (JNK) and glycogen synthase kinase-3β (GSK-3β) reduced the extent of tau phosphorylation levels at Thr231 and Ser202/Thr205. JNK inhibitor significantly decreased NL invagination in dSH-SY5Y-FL-Tau and -Tau35 cells. Furthermore, GSK-3β inhibition alleviated f-actin overstabilization in dSH-SY5Y-FL-Tau cells. In conclusion,

we identified that NL invagination and f-actin overstabilization could be modulated by inhibition of involving kinases in tau phosphorylation. Keywords: Tauopathy, Neurotoxicity, Nuclear Lamina, Actin, Kinase Inhibitor

P2-C-394: Effects of selective estrogen receptor activation on anxiety-like behaviours observed in the Open Field Test following global cerebral ischemia in ovariectomized female rats

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One of the consequences of global cerebral ischemia (GCI; mimicking cardiac arrest) is a functional impairment that leads to altered anxiety-like behaviours. Due to declining estrogen levels, postmenopausal women face an increased risk for the development of GCI as well as heightened severity of its outcomes. As such, hormone replacement therapies are used to combat these risks. The aim of this study is to further determine whether a specific estrogen receptor (ER) agonist leads to reduced alterations of post-ischemic anxiety-like behaviours. Following a 7-day acclimation period, ovariectomies were performed on 41 female Wistar rats. Rats then received daily injections of propylpyrazole triol (PPT; ERα agonist, n=7), diarylpropionitrile (DPN; ERβ agonist, n=8), G-1 (GPER; G-protein coupled ER agonist, n=7), 17β-estradiol (n=8), or vehicle solution (n=6) over a period of 3 weeks. Rats were then subject to GCI using the four-vessel occlusion model, or sham surgery (n=6, receiving vehicle solution). After recovery, a 10-minute Open Field Test (OFT) assessed anxiety-like behaviours. One-way ANOVA showed increased rearing in GPER-treated rats in the first 5 min compared to vehicle-treated rats. The ERβ-treated group tended to show reduced exploration of the peripheral zone in the first 5 minutes while GPER rats showed reduced centre zone exploration in the last 5 minutes. In sum, aside minimal alterations, GCI or ER agonist treatment was not associated with changes in anxiety-like behaviours in the OFT in this study, possibly related to increased handling of the rats.

P2-C-395: Longitudinal changes in cerebral metabolism and blood flop associated with levodopa induced dyskniesa development in a parkinsonian rat model

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Levodopa is a highly effective treatment for Parkinson's disease (PD), but comes with the risk of the patient developing a motor complication known as Levodopa induced dyskinesia (LID). Dissociation in the hemodynamic and metabolic response in the basal ganglia upon L-DOPA treatment may predict dyskinesia onset. 20 Sprague Dawley rats underwent 6-OHDA lesion of the substantia nigra to induce parkinsonian symptoms. Animals received 2 mg/kg L-DOPA per day and dyskinesia symptoms were assessed after L-DOPA on days 1, 11, and 21 by behavioral test. Cerebral metabolism and blood volume were measured by imaging with Fluorodeoxyglucose positron emission tomography and dynamic susceptibility contrast MRI respectively. Animals were scanned on day 1 and day 22, both off L-DOPA and after L-DOPA treatment. 7 animals developed LID symptoms, while 13 animals remained non-LID. In the non-LID animals, L-DOPA treatment significantly reduced FDG uptake in the lesioned hemisphere of the

striatum (lesioned side p = 0.009; non-lesioned side p=0.031), which persisted after 22 days of treatment. (lesioned side p = 0.07, t=2.029; non-lesioned side p=0.097). In contrast, L-DOPA failed to reduce FDG uptake in the same region in LID animals, either at baseline or after 22 days of treatment. In the LID animals only, striatal blood volume was significantly increased ON-L-DOPA after 22 days of chronic treatment, which was not observed at baseline (lesioned hemisphere, p=0.042; non-lesioned hemisphere, p=0.028). non-LID animals were distinguished from LID animals by L-DOPA dependent reductions in striatal metabolism at the first dose of L-DOPA. Increases in cerebral blood volume distinguished LID animals from non-LID, however this increase developed later and was not present from the first dose.

P2-C-396: A non-hallucinogenic LSD analogue with therapeutic potential in mood disorders

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Serotonergic psychedelics are emerging as alternative therapies for treatment-resistant depression, however, their hallucinogenic potential limits widespread clinical use. Second-generation psychedelics, which lack hallucinogenic effects, are a promising alternative. 2-Bromo-LSD (2-Br-LSD/BETR-001) is an LSD derivative with 5-HT2A partial agonist activity that lacks hallucinogenic effects. Thus, 2-Br-LSD may represent a possible novel therapeutic for treating neuropsychiatric diseases. We assessed the effects of 2-Br-LSD on stress-coping behaviour in chronically stressed, or stress-naïve, mice, using Forced-Swim and Open-Field tests. This was followed by Golgi-Cox staining and imaging to evaluate neuroplastic correlates. We also tested the effect of 2-Br-LSD on neuroplasticity in primary rat cortical neuron cultures using immunofluorescent imaging. Finally, we tested if the 5-HT2A antagonist, Volinanserin, could reverse these effects. In culture, 2-Br-LSD induces dendritogenesis, an effect blocked by Volinanserin, and spinogenesis. In stress-naïve male and female mice, 2-Br-LSD increases active-coping behaviour, which is also blocked by Volinanserin. Further, the behavioral effects of 2-Br-LSD correlated with improved spine density in the prefrontal cortex. Finally, 2-Br-LSD reverses the effects of chronic stress on open field exploration and self-grooming behaviour. Our findings demonstrate that 2-Br-LSD induces cortical plasticity in vitro and in vivo, promotes active stress-coping behaviours, and reveres the behavioural effects of chronic stress. These results show that 2-Br-LSD possesses therapeutic potential and represents a promising alternative to classic psychedelics in treating depression.

P2-C-397: Understanding the role of SYNGAP1 in Parvalbumin-expressing GABAergic Circuit Development and Function

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Introduction: Haploinsufficiency of Syngap1 gene encoding the Synaptic Ras-GTPase Activating protein is associated with intellectual disability, autism spectrum disorder and epilepsy. Mouse models of Syngap1

haploinsufficiency show alterations in synaptic plasticity, behavioural abnormalities and cognitive deficits. Several studies have shown that Syngap1 regulates the developmental trajectory and function of excitatory neurons; in contrast, the role of Syngap1 in inhibitory GABAergic neurons is less well understood. GABAergic neurons are a diverse class of neurons with different morphology, connectivity and physiological properties. Parvalbumin (PV)-expressing interneurons, one of the major classes of cortical GABAergic interneurons, form synapses onto the soma and proximal dendrites of pyramidal cells and play an important role in neural circuit development and plasticity. Objective: We aim to understand the role of Syngap1 expressed by PV cells in sensory processing and cognition. Method: We used both a) Nkx2.1 Cre conditional mice to specifically delete Syngap1 embryonically in interneurons derived from the medial ganglionic eminence (where PV and somatostatin-expressing interneurons originate), and b) PV Cre conditional mice to specifically delete Syngap1 postnatally in PV cells respectively. Results: Our results suggest altered social behavior and fear extinction, specifically in Nkx2.1Cre:Syngap1lox but not in PVCre:Syngap1lox mutant mice. Further we found Nkx2.1Cre:Syngap1lox mice show specific alterations in auditory processing. Conclusion: Haploinsufficiency of Syngap1 in interneurons can thus contribute to cognitive alterations caused by Syngap1 mutations during development.

P2-C-398: Alpha-synuclein aggregation in parkinson's disease

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Parkinson's Disease (PD) is the second most common neurodegenerative disease in the world. One of the major pathological hallmarks of the disease is the aggregation of a misfolded protein called alpha-synuclein (a-syn), which will lead to the formation of cellular inclusion known as Lewy bodies. However, how these aggregates disturb neuronal homeostasis leading to neurodegeneration remains elusive. Several studies showed a correlation between alterations of degradation systems (autophagic or proteasomal), implicated in the protein quality control, and a-syn aggregation. Nevertheless, it is not clear yet how the degradation is impaired. Our aim is here to know precisely how an alteration of the degradation systems is involved in the pathogenesis of PD. To study the effect of a-syn aggregation, the LIPA (Light-Inducible Protein Aggregation) system recently developed by our laboratory is used. This system nicely mimics key features of Lewy bodies and allows to optogenetically control and observe in real time the aggregation of a-syn. Using this model, we were able to observe for the first time the effect of LIPA-induced aggregates on proteasome and autophagy systems by using specific markers. Moreover, we also get interested in inhibiting these systems and the effect on the aggregation. The results obtained show us the capacity of our LIPA system to mimic the potential effects of a-syn on the degradation systems. Taken together our observations reveal the impact of autophagy and proteasome dysfunctions in PD pathogenesis. Interestingly, we found that both systems seem involved but in a different manner and with a different kinetic.

P2-C-399: Effects of intranasal insulin on memory and physiology in the 5xFAD mouse model of Alzheimer's disease

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As well as a disorder of cognitive function, Alzheimer's Disease (AD) is a metabolic disorder related to insulin resistance in the brain and has been termed "type 3 diabetes". Intranasal insulin administration has been proposed as a treatment for AD. The 5xFAD mouse shows age-related decreases in body weight as well as cognitive and motor deficits. As defective insulin signaling in AD is an example of metabolic dysregulation, this study examined whether intranasal delivery of insulin (INDI) at low (LI; 0.875 U) and high (HI; 1.75 U) doses would ameliorate these deficits compared to saline (S) in 12-month-old female 5xFAD and WT (B6SJL) mice. The 5xFAD mice had poorer performance on the balance beam than WT mice ($p < 0.05$) and there was no effect of insulin. The HI group performed better than the saline group in the novel object recognition test ($p < 0.05$) and showed better memory performance in the probe trial of the Morris Water Maze test. Although INDI had no significant effect on body weights, HI doses of INDI increased the liver, spleen, and kidney weights in both WT and 5xFAD mice ($p<0.05$). Brown adipose tissue weights in the HI group were lower than in the S and LI groups. P-Akt signaling was increased by INDI in a dose-dependent manner ($p < 0.05$). These findings indicate that visuo-spatial memory and organ weights in female 5xFAD mice are affected by treatment with intra-nasal insulin in a dose dependent manner.

P2-C-400: Therapeutic effect of the mGlu2/3 orthosteric agonist LY-404,039 in the MPTP-lesioned marmoset model of Parkinson's disease

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LY-404,039 is an orthosteric agonist of metabotropic glutamate 2/3 (mGlu2/3) receptors that may possess an additional agonist effect at dopamine D2 receptors. We recently showed the therapeutic effect of mGlu2/3 orthosteric stimulation on dyskinesia and psychosis-like behaviours (PLBs) in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset model of Parkinson's disease (PD), although the administered molecule was devoid of action at D2 receptors. Here, we aimed to determine the effect of LY-404,039 on dyskinesia, PLBs, and parkinsonism in the MPTP-lesioned marmoset. Marmosets were rendered parkinsonian by injections of MPTP. Following a month-long recovery period, dyskinesia and PLBs were elicited by daily treatment with L-DOPA. On experiment days, marmosets were injected L-DOPA with either vehicle or LY-404,039 (0.1, 0.3, 1, and 10 mg/kg). Marmoset behaviours were recorded and analysed post hoc for parkinsonism, dyskinesia and PLBs. When added to L-DOPA, LY-404,039 10 mg/kg significantly reduced global dyskinesia (55%, $P < 0.01$) and PLBs (50%, $P < 0.05$), and significantly enhanced the anti-parkinsonian action of L-DOPA (47%, $P < 0.05$). Our results show that LY-404,039 is efficacious at alleviating dyskinesia, PLBs, and parkinsonism in the parkinsonian marmoset and reinforce the paradigm of orthosteric stimulation of mGlu2/3 for diminishing dyskinesia and PLBs. In addition, the possible agonistic effect of LY-404,039 at D2 receptors might represent an additional therapeutic asset. As LY-404,039 and its pro-drug, LY-2140023, have

previously entered clinical trials as treatment for schizophrenia, they could be quickly repurposed as a treatment for PD.

P2-C-401: Gonadotropin-inhibiting hormone and gonadotropin-releasing hormone expression is upregulated in the ischemic brain

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Gonadotropin-releasing hormone (GnRH) and gonadotropin-inhibiting hormone (GnIH) are neuropeptides which work to regulate the hypothalamic-pituitary-gonadal (HPG) axis and the associated estrous cycle. Global cerebral ischemia (GCI), mimicking cardiac arrest, induces numerous functional alterations throughout the brain, but its impact on the HPG axis remains largely unknown. The goals of this study were to determine if GnRH and GnIH expression are affected by GCI, and to characterize estrous cycle regularity post-ischemia. Methods: Adult female Wistar rats underwent vaginal lavage for 2 weeks before being subjected to GCI for 10 minutes or sham surgery. Estrous cycle was monitored for 24 days post-surgery, after which rats were euthanized. Immunofluorescence detected GnIH and GnRH expression in the arcuate nucleus (ARC) and medial preoptic area (POA) of the hypothalamus, as well as the CA1 of the hippocampus. Results: Following surgery, 87.5% of ischemic rats presented a disrupted cycle (persistent diestrus, average length 11.86 days), before resuming regular cycling. T-tests revealed a significant up-regulation of GnIH percentage of area in the CA1, and GnRH percent area in the ARC of GCI rodents. A trend for higher GnIH mean grey value and significantly higher GnRH mean grey value in the CA1 of GCI rodents was also observed. Conclusion: Overall, our results highlight that expression of GnRH and GnIH is affected in the CA1 and ARC following GC1. As HPG axis dysregulation persists up to one month after GCI, this points to possible long-term impacts on the reproductive axis.

P2-C-402: Investigating the consequences of wild type huntingtin deletion in the adult mammalian hippocampus

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Huntington's disease (HD) is a fatal neurodegenerative disease that emerges from a CAG repeat expansion in the huntingtin (HTT) gene, resulting in the production of a mutant huntingtin protein (mHTT). Non-pathogenic wild type HTT (wtHTT) is critical for embryonic development and has hundreds of interacting partners involved in diverse cellular functions. Importantly, wtHTT has been suggested as a major regulator of synaptic homeostasis. However, the role of wtHTT at mature synapses and the consequences of wtHTT loss on synaptic function remain unclear. To investigate the effect of wtHTT loss on synaptic plasticity, wtHTT was conditionally deleted in the hippocampus of 2-4 month-old Httfl/fl mice by AAV-Cre injection. wtHTT conditional knockout (cKO) was confirmed by Western blot methods, and we found that 1-2 month deletion significantly impaired both post-tetanic and long-term potentiation at Schaffer collateral synapses. Anecdotally, we were also unable to evoke and maintain fEPSP responses in wtHTT cKO animals 6-8 months post-injection, while responses were normal in age-matched controls.

We are now assessing hippocampal-dependent learning and memory, as well as anxiety and depressive-like behaviours, in Httfl/fl mice 6-8 months post-injection using a comprehensive behavioural paradigm. Perfused hippocampal tissue from these animals will also be IHC stained post-behaviour for synaptic profiling using super-resolution imaging techniques. Understanding the consequences of wtHTT loss in the adult brain is critical as many HD genetic therapies currently in clinical trials further lower patient wtHTT levels, which may have unknown negative effects.

P2-D-403: Vestibular signals influence reach trajectory selection during simulated body motion

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Vestibular signals have been shown to contribute to reach planning and execution during body motion. However, less is known about how they contribute to action selection. Here we tested the hypothesis that vestibular signals influence the choice of trajectory around an obstacle and that this influence is mediated by distinct mechanisms during reach planning vs. execution. Human subjects reached in darkness to a remembered target while avoiding collision with a remembered obstacle placed between the start position and target. Subjects were free to choose whether to avoid the obstacle by reaching around it to the left or right. Galvanic vestibular stimulation (GVS) was applied on pseudo-random trials to simulate body motion. We predicted that GVS applied before reach onset would increase the proportion of choices relative to no stimulation controls in the same direction as the simulated motion, consistent with vestibular influences on "spatial updating" mechanisms during planning. In contrast, we predicted that GVS applied during reaching would increase the proportion of choices in the opposite direction to the simulated motion, consistent with vestibular influences on online correction mechanisms. In agreement with these predictions, choices were biased in the direction of simulated motion when GVS was applied before reach onset but in the opposite direction when GVS was applied during reach execution. These results suggest that vestibular signals contribute to trajectory selection and that this is mediated via distinct mechanisms during reach planning vs. execution.

P2-D-404: Effects of isoflurane anesthetic on the auditory brainstem response of domestic cats

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Isoflurane is an anesthetic commonly used in neurobiological investigations involving animal subjects. It is easy to administer, quick to act, and helps minimize artifacts during electrophysiological recordings. Yet, isoflurane has been found to have a dulling effect on auditory pathway activity in rodents, such as mice, rats, and guinea pigs. However, its influence on the domestic cat (Felis catus) auditory system is unclear. In this study, we evaluated the effect of isoflurane on the auditory activity in cats using an objective assessment of hearing sensitivity: the auditory brainstem response (ABR). The ABR was used to assess the integrity of the auditory pathway. During the procedure, different auditory stimuli were presented, which leads to a response that reflects activity in the auditory nerve and subsequent brainstem nuclei. We performed ABR recordings by presenting broadband stimuli to each cat (n=6) at

intensities from 20-80dB while administering isoflurane in a continuous stream of O2, in incremental levels from 0-2%. We report the changes in ABR amplitude, threshold and latency. Understanding the effect of isoflurane on domestic cat ABR could help better interpret how its administration might influence other auditory data collected in anesthetized cats. A more accurate report of the effects of isoflurane in different animal models could help draw comparisons on the interpretations of auditory research in other species. Lastly, this research could elucidate whether certain neuroanatomical sites are more susceptible to different concentrations of isoflurane.

P2-D-405: Brainstem regions activated during cortical stimulation-induced mastication in mice

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The core of the masticatory central pattern generator (CPG) lies between the rostral pole of the trigeminal (NVmt) and the facial (NVII) motor nuclei. The minimal critical area to produce rhythmical output, a key feature of CPGs, includes trigeminal primary afferent (NVmes), premotor interneurons of the peritrigeminal area (PeriV), trigeminal main sensory nucleus (NVsnpr) and the rostral pole of spinal nucleus (NVspo). Previous work from the laboratory has identified a population of neurons in the dorsal part of the (NVsnpr) which firing pattern changes from tonic to rhythmic when the extracellular calcium concentration decreases and enhances a persistent sodium current. While it was suggested that they form the core of masticatory CPG, we do not know whether other populations of neurons in the brainstem also contribute to the genesis of the masticatory rhythm and project to different populations of motoneurons. To address these questions, we used transgenic mice expressing ChR2 under the control of VGluT2 or Thy1 neuronal promoters. Rhythmic jaw movements were elicited in awake animals using right unilateral 40Hz optogenetic stimulation of the cortical masticatory area of 3 seconds every 30 seconds for 30 minutes, followed by a 60-minute rest period for peak expression of the cellular marker of activity c-fos. Animals were sacrificed and c-fos analysis were performed on brainstem slices from the hypoglossal nucleus to the NVmt. Preliminary data revealed that c-fos expression was elevated in neurons of the PeriV, suggesting the involvement of this region during mastication.

P2-D-406: Probing the cerebellar contribution to aging using chemogenetics

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Declines in motor coordination are common in aging and limit one'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 may contribute to the decline in motor coordination we observed. To determine if Purkinje cell firing alterations directly contribute to motor dysfunction in aging, we virally delivered chemogenetic receptors to modulate Purkinje cell spiking activity. We found that chemogenetic reduction of 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-407: Parvalbumin controls inhibitory tone in the dorsal horn of the spinal cord

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The central nervous system (CNS) processes sensory information by relying on the precise coordination of neural networks and their synaptic firing patterns. In the spinal cord, disturbances to the firing pattern of the tonic firing parvalbumin-expressing inhibitory interneuron (PV neurons) disrupt the ability of the dorsal horn (DH) to integrate touch information and may result in pathological phenotypes. The parvalbumin protein (PVp) is a calcium (Ca2)-binding protein that buffers the accumulation of Ca2 following a train of action potential to allow for tonic firing. Here, we find that peripheral nerve injury causes a decrease in PVp expression in PV neurons and transitions them from tonic to adaptive firing. We show that reducing the expression of PVp causes otherwise healthy mice to develop mechanical allodynia. This critical role for PVp extends outside of the DH and applies to other CNS PV neurons. Indeed, in both the DH and hippocampus, decreasing PVp causes the PV neurons to lose their high frequency activity. We show that this transition is mediated by Ca2 -activated potassium (SK) channels activation in PV neurons of the DH and hippocampus. Further, their tonic firing can be partially restored after nerve injury by selectively inhibiting the SK2 channels in DH PV neurons. By preventing the decrease in PVp expression before nerve injury, we were able to protect mice from developing mechanical allodynia. Our data indicate an essential role for PVp-mediated calcium buffering in PV neuron firing activity and in mechanical allodynia after nerve injury.

P2-D-408: The gain of the optomotor response varies across the visual field during hovering flight in hummingbirds

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During hovering, hummingbirds rely on global visual motion cues to stabilize their position in space. When large field stimuli are presented in the frontal visual field, hovering hummingbirds will drift in the corresponding direction. In a previous study, gratings were used to elicit up-, down-, left-, and right-drifts. Looming and receding spirals were used to elicit backwards and forwards drifts, respectively. Hummingbirds have a nearly 360° visual field, but their fovea is oriented laterally and their area temporalis, which has lower spatial resolution, is oriented forwards. These features led us to ask

whether the gain of the optomotor response varies in different regions of the visual field. We created a square arena with screens on all four walls, and presented hovering Anna's hummingbirds (Calypte anna) with looming or receding spirals. Several combinations were tested including single, opposite, and adjacent screen presentations. Bird head positions were recorded using a 3D motion capture system. We found that responses were strongest when the stimulus was more frontal and waned as it shifted posteriorly. Responses to two-plane cues tended to be muted relative to responses to single plane cues, regardless of location in the visual field. The largest responses occurred when stimuli were centered within the projection regions of the fovea and the area temporalis. We observed few hovering bouts where birds centered stimuli within their narrow binocular visual field. Additional experiments are planned to investigate the roles of different regions at a finer scale.

P2-D-409: Processing of the accuracy response in the cortical visual area 21a.

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Our vision is provided by a succession of hierarchical areas containing neurons selectively sensitive to different characteristics of visual stimuli. As the cortical hierarchy progresses, neurons become increasingly selective and sensitive to complex patterns. Recently, our laboratory characterized the dynamics of the orientation responses of neurons of the cat primary visual cortex, V1, using natural stimuli. These experiments showed that very slow dynamics are involved in the processing of low precision patterns. How accuracy affects orientation in higher hierarchical areas is unknown. Here, we studied the difference in response to accuracy in a higher-order cortical area, more precisely in area 21a in the cat, often considered as the homologue of the primate area V4. We hypothesized that, if accuracy follows a hierarchical organization, neurons in 21a will have an amplified (linear) response to accuracy compared to those in V1. We used pseudo-natural visual stimuli with controlled accuracy content, MotionClouds, and recorded the responses of neurons in area 21a to quantified variations in orientation accuracy. Preliminary data indicate that the tuning curve of neurons stimulated with Motion Clouds have amplified response to accuracy compared to those in V1. This data suggests that the cortical ventral stream is involved in accuracy processing.

P2-D-410: Changes of interocular suppression and contrast sensitivity that underlie ocular dominance changes induced by short-term monocular deprivation in control and amblyopic individuals

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The standard treatment for amblyopia, a neurodevelopmental disorder with monocular and binocular visual function deficits, is to deprive the fellow eye for 3-6 hours a day. However, this approach is not beneficial for binocular vision. To understand the neural basis of the neuroplastic effect of monocular deprivation, we investigated the changes in suppressive interocular interactions and monocular contrast threshold before and after 2 hours of monocular deprivation. Nine amblyopes and 10 control adults

participated in our study. Interocular suppression and contrast sensitivity were measured using a dichoptic masking paradigm before and after the monocular deprivation. We demonstrate that the ocular dominance changes that occur as a result of short-term monocular deprivation, namely the strengthening of the deprived eye contribution, are associate with asymmetric changes in interocular suppression where the suppression from the nondeprived eye is reduced. Similar results occur in normals and amblyopes. But in amblyopes, the reduction of suppression from the nondeprived eye is larger than that from the deprived eye; while in normals only the suppression from the nondeprived eye showed reduction. The changes in contrast sensitivity are symmetric between the eyes with the previously deprived eye's sensitivity being increased and the nondeprived eye's sensitivity being reduced in both controls and amblyopes. This provides a better understanding of how inverse patching (patching of the amblyopic eye) could form the basis of a new treatment for the binocular deficit in amblyopia.

P2-D-411: Influence of a visual landmark shift on memory-guided reaching in monkeys

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The brain uses various sources of visual information, including both egocentric and allocentric to aim movements. It has been shown that humans optimally weigh egocentric and allocentric (landmark) cues when pointing (Bryne & Crawford 2010) but it is not known if monkeys do this. The main purpose of this study is to determine the influence of allocentric cue shifts on reaching responses in non-human primates. In order to do this, reach and gaze data were collected from one female Macaca mulatta monkey (ML) trained to perform a memory-guided reaching task. The hand was initially placed at 1 of 3 locations of a waist level LED bar while gaze fixated centrally. A landmark (4 'dots' spaced 10° apart) was then presented at 1 of 15 locations on a touch screen after a delay. A visual target then appeared transiently at a variable location within this landmark, followed by a visual mask. After the mask, the landmark either reappeared at the same location (stable-landmark condition) or shifted by 8° in one of 8 directions (landmark-shift condition). The fixation light then extinguished, signaling a reach to the target. 'No-landmark' controls were the same, but without the landmark. Reaches correlated (r =0.45) with target location relative to landmarks, showing animals did not simply reach to the landmark. Correlations for reach and gaze were poor (r =0.05). Reach had lower variance and was better correlated to targets than gaze suggesting gaze was not used to guide reach in this task. In the landmark-shift condition, reaches shifted partially (mean=23%) with the landmark. Overall, this data suggests that the monkey is influenced by visual landmarks when reaching to a remembered target in a similar way as humans.

P2-D-412: Sex- and hormone-dependent recruitment of cortical fast-spiking inhibitory neurons during auditory stimulation in mice auditory cortex

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Altered brain responses to auditory stimulation (AS) are currently explored as translational biomarkers of neurodevelopmental disorders; however, the underlying neuronal mechanisms and potential sex-related differences of these evoked responses are still not well understood. In humans, auditory sensitivity, predictive coding and repetition suppression to sounds have been shown to change over the woman's reproductive cycle. Recent studies in mice have shown that excitability of fast-spiking (FS) cells, a subgroup of cortical GABAergic cells playing a critical role in auditory processing, fluctuates over the estrous cycle in female mice. Here, we hypothesize that changes in hormonal concentrations during the estrous cycle affect auditory perception in female mice by modulating FS cells firing. To investigate this question, we perform multielectrodes extracellular recordings from the primary auditory cortex in awake mice. Our results reveals several aspects of auditory processing, including habituation to repetitive auditory stimuli and auditory entrainment at 40Hz are dependent on the phase of the estrous cycle in females. We are currently investigating FS cell firing dynamics during different AS tasks. Our preliminary results on spiking activity shows an increased firing and spike-lfp coherence of FS inhibitory neurons during estrous phase in females suggesting changes in auditory perception during the estrous cycle could be explained by a prefered recruitment of cortical FS interneurons in the primary auditory cortex. Altogether, these data will shed light on the circuit and functional basis of normal and abnormal auditory processing in males and females, which may in turn help to explain sex-differences in psychiatric disorders.

P2-D-413: Do auditive stimulations, at a given frequency, can promote brain oscillation? a protocol study

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Recent studies showed that transcranial alternating current stimulation (TACS) promotes brain oscillation at a specific frequency including somatosensory evoked potentials from peripheral median nerve stimulation (SSEPm) and brainstem auditory evoked potentials (BAEP). The main goal of this study is to investigate whether we can achieve similar SSEPm and BAEP modulation with 10 Hz auditory stimulation as with 11 Hz TACS. Fifteen healthy participants exempt from a history of neurological/sensitive/hearing deficits will be enrolled in a crossover 2-arm randomized study. All participants will undergo SSEPm and BAEP recording pre- and post-stimulation. SSEP electrical current will be applied on median nerves at the wrist using three blocks of 1000 repetitions of a 200 µs electrical current at 3 Hz. Recording electrodes will be placed at Erb point bilaterally, C7 spinous process, and Fz, Cz, C3' and C4' according to the 10-20 international system. BAEP will consist of 70 dB clicks of 100 µs each at 8 Hz. Three blocks of 2000 repetitions will be used. Electrodes will be placed on both ear lobes and Cz. Arm 1: TACS will be applied over the primary motor cortex at 10Hz for 20 min. Arm 2: a familiar voice saying the vowel A will be heard at 10Hz for 20 min. Both arms will be separated by a 48h washout period. Difference post and pre-stimulation will be calculated for each participant and groups will be compared using t-test. This project could help to develop a new technique to induce frequency-based brain oscillation which could be easily implementable in a clinical setting.

P2-D-414: Functional investigation of glutamatergic neurons of medullary reticular formation nuclei in locomotor recovery after spinal cord injury

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The medullary reticular formation (mRF) is an extensive part of the brainstem controlling variety of motor and locomotor functions. Although anatomical studies have shown the plasticity of reticulospinal axons or neurons after spinal cord injury (SCI), little is known about their neurotransmitter phenotype and their functional contribution to locomotor recovery. Using kinematic and electromyographic measurements in transgenic mice, we investigated changes in locomotor functions upon photostimulation of glutamatergic neurons of different mRF nuclei. Before SCI, long trains of photostimulation for 1 s led to different locomotor behaviors including initiation, acceleration, pause, or locomotor arrest depending on the stimulation site within the mRF. Seven weeks after SCI, some of these sites kept their functional effects, whereas others exhibited plasticity with the emergence of new functions. Furthermore, in chronically impaired mice, long trains of photostimulation reduced the variability in locomotor stepping and normalized to pre-injury levels the position of the ankle prior to the swing phase, thus improving locomotion. In summary, our findings show that glutamatergic neurons of the mRF contribute to locomotor recovery after SCI and can improve functional outcomes after chronic SCI. Funding: Craig H. Neilsen Foundation and Wings for Life Foundation

P2-D-415: Precision in the pacemaker nucleus of weakly electric fish

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Neural oscillations play a critical role in brain information processing, including decision making, learning and memory processes, and neural communication. In these contexts, reliability and precision of the underlying neural activity can be critical, especially in response to a stimulus. In weakly electric fish (Apteronotos leptorhynchus), the medullary pacemaker network (Pn) sets the timing of an electric organ discharge (EOD) used for electric sensing. Among all biological rhythms, the electric organ discharge (EOD) is the most precise, with sub-microsecond variations in cycle period and a coefficient of variation (CV = standard deviation/mean period) of ~10^-4. How the Pn, a network of only 150 neurons with weakly gap junctional coupling, can achieve such high precision is not clear. One hypothesis is that Pn activity is regularized by electrical feedback from the EOD itself. As a first step toward testing this, we use a computational approach to investigate the impact of an electric field on the variability of an individual pacemaker cell under various conditions. We simulate the activity of a model pacemaker neuron and mimic the electric field effect as an auto-feedback stimulus with a delay. Our results show that the effect of electric field feedback either increases or decreases the CV of the period, depending on the amplitude and delay.

P2-D-416: The influence of anesthesia on avian pretectal optic flow responses

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Animal locomotion is a multi-sensory behaviour. Many animals including birds and humans, depend on global visual motion, commonly termed optic flow, to guide movement through natural environments. In all tetrapods, the midbrain contains two retina-recipient areas that respond to optic flow stimuli, and demonstrate tuning with respect to direction, speed, and in the spatiotemporal domain. In mammals, these areas are termed the terminal nuclei of the accessory optic system and the nucleus of the optic tract of the pretectum. In other tetrapods, they are referred to as nucleus of the Basal Optic Root (nBOR) and the nucleus lentiformis mesencephali (LM), respectively. Electrophysiological characterization of these neurons is typically performed under anesthesia, so it is unclear how these neurons may be involved in the visual guidance of locomotion. We performed head-fixed extracellular recordings from LM with simultaneous eye tracking during three states: 1) gas anesthesia (isoflurane); 2) injectable anesthesia (ketamine/xylazine), and when awake. These experiments revealed differences among all three conditions. Isoflurane suppressed LM neural activity, causing neurons that otherwise have relatively high background firing rates to become silent. Ketamine/xylazine altered baseline activity but produced similar tuning properties to the awake condition. These findings suggest that anesthesia may blunt or otherwise influence multi-sensory or motor-dependent inputs involved in optic flow processing.

P2-D-417: Sex differences in contribution of Na/K/Cl co-transporter and GABA receptors in chloride homeostasis of c-fiber primary afferents in the spinal cord dorsal horn.

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[Cl-]i is high in primary sensory neurons due to the activity of the NKCC1, causing greater Cl- accumulation in PNS neurons. Thus, central terminals of primary afferents in the spinal dorsal horn experience depolarization upon activation of GABAA receptors. Thus, regulation of [Cl-]i in these terminals may significantly affect transmitter release. Determining the exact [Cl-]i in C-fiber terminals is pivotal to understand sensory processing. To image [Cl-]i we used superclomeleon, which was virally transduced selectively in C-fibers in SNS-cre, MRGPRD-cre and TRPV1-cre mice. We did 2-photon microscopy in acute spinal cord slices and on the acutely delaminated spinal cord in anesthetized 2, 4, and 6 months old 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. NKCC1 protein and mRNA levels in the dorsal root ganglia were evaluated with western blot and RNAScope. Also, we recorded local field potentials in spinal cord slices of WT mice. We found significantly higher [Cl-]i in non-peptidergic than peptidergic C-fibers, which both were significantly higher in different age males than females. Bumetanide decreased [Cl-]i significantly more in males compared to females. Bicuculline increased [Cl-]i significantly more in C-fibers in females compared to males. NKCC1 protein and mRNA were also significantly lower in females than in males. We revealed that in slices of WT mice, paired-pulse ratio of local field potential is bigger in males, which bicuculline could

abolish it. Presynaptic inhibition appears to be under distinct control by GABAergic inhibition and NKCC1 function between sexes, which should be taken into consideration in future studies.

P2-D-418: Whole brain mapping of long-range monosynaptic inputs to different primary motor cortex cell types

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The primary motor cortex (M1) receives long-range inputs from multiple cortical and sub-cortical areas which are integrated in its intricate local microcircuitry composed of pyramidal neurons (PNs) and diverse inhibitory interneurons (INs) subtypes. The way through which these long-range inputs recruit different cell types in M1 needs to be elucidated in order to better understand how computations within M1 can give rise to a myriad of sophisticated motor behaviors. To reveal these long-range monosynaptic inputs to different M1 cell types, we applied a monosynaptic rabies tracing system to Cre driver mouse lines labeling either PNs, somatostatin-, parvalbumin-, or vasoactive intestinal peptide-expressing inhibitory neurons (SST-INs, PV-INs and VIP-INs, respectively). We then used an automated cell counting pipeline aligned to the Allen Atlas to quantify the monosynaptic inputs from the whole brain onto the different cell types of M1. We found that while all cell types received major inputs from sensory, motor, and prefrontal cortical regions, as well as from various thalamic nuclei, VIP-INs received more inputs from the orbital frontal cortex (ORB) - a region associated with reinforcement learning and value predictions. In contrast, SST-INs received more input from the retrosplenial cortex (RSP), demonstrating that different IN subtypes receive preferential long-range input from specific brain regions. Our findings provide insight on how the brain leverages microcircuit motifs by both integrating and partitioning different streams of long-range input to modulate local circuit activity and plasticity.

P2-D-419: The molecular mechanism for the pain caused by lionfish venom

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The wealth of biodiversity in the world's library of venoms and their toxins represents an enormous untapped resource that could contain the scaffolds for a nearly infinite number of therapeutic drugs. Within the realm of venoms that have been studied, marine venoms represent only a small minority in comparison to those of insects and snakes. The red lionfish (Pterois volitans) is a venomous species of fish originating from the Indo-Pacific but now invasive in many regions, where it poses a significant stress on marine ecosystems and produces one of the most painful stings in the ocean. Prior to our work, there was almost no understanding of the pain-causing mechanism of action of the venom. Through electrophysiology and calcium imaging experiments, we have identified the receptor target of the venom, and are identifying the pain-causing component of the venom. Furthermore, we have cloned the receptor target of the venom from a predator of the lionfish - the moray eel - and are characterizing this receptor's sensitivity to lionfish venom to identify the molecular mechanism for its resistance. There is

an enormous demand for the development of novel pain treatments, since most that exist are either inefficient or addictive. By studying lionfish venom and identifying how it causes pain, we can start to develop novel pharmaceutical agents for the specific and efficient treatment of pain conditions.

P2-D-420: Sensorimotor cortex reorganization following photothrombotic motor cortex stroke in mice

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Background - We used non-invasive light-based motor mapping (LBMM) and intrinsic signal optical imaging (ISOI) to reveal stroke-induced changes in forelimb motor and sensory representations during recovery. Our objective is to identify regions within the sensorimotor cortex that show re-mapping associated with behavioural recovery. Methods - LBMM utilized blue-light stimulation of the cortex to induce forelimb movements. Evoked responses were recorded to generate heat maps. Within the same mice, ISOI was used to record the cortical hemodynamic response to forelimb vibrotactile stimulation, and sensorimotor forelimb function was assessed with the cylinder, grid walking, and string-pulling tasks. Assessments were conducted at baseline and at weekly intervals following a photothrombotic stroke in M1. Results - A stroke targeting M1 produced lasting impairments in motor maps. Although movements derived from the injured hemisphere showed partial recovery, motor map representations never reached baseline values. Movements derived from the intact hemisphere were also decreased after stroke, however, returned to baseline values within 3 weeks. ISOI revealed a temporary impairment in sensory representation post-stroke. Behavioural analyses show impairments last 4-5 weeks in duration. Conclusion - Utilizing longitudinal LBMM and ISOI we find an increase in both peri-infarct and contralesional motor representations post-stroke, while sensory representations were less impacted. Together with our findings of behavioural recovery our results suggest that cortical remapping is functionally relevant during spontaneous recovery.

P2-D-421: Modelling stimulus-Induced Gamma rhythms in Monkey V1 area and Implication for Brain Stimulation.

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Fast brain rhythms (30-90 Hz), known as gamma oscillations, are ubiquitously observed in the brain areas of several species, including rats, monkeys, and humans. They have been documented to play important roles in memory, attention, and inter-areal brain communication. However, gamma rhythms recorded in some areas as the primary visual cortex (V1) of humans and monkeys are stochastic, appearing as random epochs of high synchrony called gamma bursts that make them difficult to understand or interpret. Gamma bursts and rhythm bursts, are related to brain disorders. Precisely, gamma bursts with too short duration and low amplitude are seen in people having Alzheimer's disease, while, beta (13-30 Hz) bursts with longer duration and higher amplitude are recorded in Parkinsonian patients. Theoretical models of stochastic gamma rhythms consistent with in vivo recordings and able to explain burst generation and dynamics are lacking. We fill this gap by deriving an envelope-phase decomposition of

the rhythms generated by an excitatory-inhibitory network. The resulting envelope-phase equations contain only two meta-parameters. This allows a straightforward fitting to various visual stimuli-induced gamma rhythms in the monkeys V1 area. Our modelling reproduces the data and can explain how different visual stimuli shape gamma burst dynamics and statistics (burst duration, amplitude, and frequency). Most interesting, our results establish a relationship between stimuli and burst properties. This opens the door to brain disorders treatment via external stimulation. The theory can be adapted and extended to other brain areas and frequency bands like beta rhythms generated in the Subthalamic Nucleus (STN), with a possible application to Parkinson's disease.

P2-D-422: Visually evoked potentials (VEPs) elicited by motion-onset stimuli in the hearing and deaf

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When deprived of a sensory modality, the brain often compensates with supranormal performance in other intact sensory systems. This phenomenon is known as cross-modal plasticity, where areas of the brain responsible for the lost modality are reorganized and repurposed to the benefit of the remaining modalities. Deaf humans and cats have superior visual motion detection abilities, and this advantage has been causally demonstrated to be mediated by reorganized auditory cortex. The present study sought to determine the electrophysiological response of hearing and deaf cats to motion-onset stimuli of different velocities. Deafness was induced in the first postnatal month by systemic administration of ototoxic drugs. In maturity, we examined VEPs in both hearing and deaf cats generated from electroencephalogram (EEG) recordings in lightly anesthetized subjects. VEPs are an averaged and amplified record of the gross electrical action potentials generated by the brain in response to visual stimulation. In both groups, peak amplitudes increased with increasing stimulus speeds, and significantly larger peak amplitudes were observed in deaf subjects at higher speeds. Cross-modal reorganization in auditory cortex underlying the significant improvement of motion detection found in deaf subjects could be contributing to the increase in neuronal discharge to visual motion stimuli, and this can lead to increased measurable VEP amplitudes.

P2-E-423: State-dependent activity dynamics of hypothalamic stress effector neurons

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The stress response necessitates an immediate boost in vital physiological functions from their homeostatic operation to elevated emergency response. However, neural mechanisms underlying this state-dependent change remain largely unknown. Using a combination of in vivo and ex vivo electrophysiology with computational modeling, we report that corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN), the effector neurons of hormonal stress response, rapidly transition between distinct activity states through recurrent inhibition. Specifically, in vivo optrode recordings in anesthetized mice show that under non-stress conditions, CRHPVN neurons often fire with rhythmic brief bursts (RB), which, somewhat counterintuitively,

constrains firing rate due to long (~2 s) inter-burst intervals. Sciatic nerve stimulation, a pain-mimicking stressful stimuli, rapidly switched RB to continuous single spiking (SS), permitting a large increase in firing rate. A spiking network model shows that recurrent inhibition can control this activity-state switch, and consequently the gain of spiking responses to excitatory inputs. In biological CRHPVN neurons ex vivo, the injection of whole-cell currents derived from our computational model recreates the in vivo-like switch between RB and SS, providing direct evidence that physiologically relevant network inputs enable state-dependent computation in single neurons. Finally, in vivo neuropharmacology showed that local antagonism of GABAA receptors, but not activation of glutamate receptors, produced model-predicted increases in continuous single spiking underlying stress-induced high activity state. Together, we present a novel mechanism for state-dependent activity dynamics in CRHPVN neurons.

P2-E-424: Investigation of the molecular consequences of chronic overactivation of hypothalamic pomc neurons in vitro

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The arcuate nucleus of the hypothalamic hosts two neuronal populations highly relevant for energy homeostasis. In a classical model, Agrp neurons drive appetite and energy sparing. Pomc neurons, on the other side, drive satiety and energy expenditure. Pomc neurons, in particular become dysfunction in a state of prolonged obesity; roughly 25-50% of them indeed disappear under conditions of long-term metabolic stress. To further understand the processes driving these changes in Pomc neurons, we developed a model to recapitulate in vitro the conditions of Pomc neurons overactivation, as seen in diet-induced obesity. To this end, we generated primary cultures of pure hypothalamic neurons, then traced and overactivated Pomc neurons using a chemogenetic approach. Here, we show how chronic activation of Pomc neurons in vitro alters their inflammatory status, their ability to generate and secrete Pomc-derived peptides, as well as how transcription factors pertaining to neuronal identity are affected.

P2-E-425: Investigating the fate of hypothalamic Pomc neurons in prolonged high fat diet

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Objective: Hypothalamic Pomc neurons play a key role in energy homeostasis by controlling satiety and energy expenditure via the melanocortin system. Pomc neurons function and integrity have been reported to be disrupted in obesity; however, a definite neuronal fate is yet to be determined. To this end we developed a novel transgenic mouse model to trace Pomc neurons on prolonged high fat diet. Methods: We generated and validated a novel transgenic mouse model of Pomc neurons tracing. Male and female transgenic mice were placed on a high fat high sucrose diet at the age of 8 weeks for a period of 4 and 8 months (ongoing) with controls to simulate human clinical long-term obesity. In parallel, to investigate the specific molecular processes determining cell fate, we also optimized a Pomc specific neuronal extraction and sorting protocol for sequencing post diet protocol. Further Pomc neuronal

chronic activation studies with viruses were also optimized. Results: We observed successful tagging of Pomc neurons and significant differences in weight in both male and female mice. We confirmed neuronal viability post extraction and viral injections by imaging. Conclusions: This study could provide insight to neurological perturbations associated with obesity.

P2-E-426: Sex specific effects of insulin modulating the relationship between early life adversity and impulsivity.

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Early life adversity (ELA) is a well-known risk factor for comorbidities between metabolic and psychiatric disorders. However, previous studies in humans and animal models raise the possibility of prominent sex differences in the effects of ELA exposure. Recent studies have shown the potential role of insulin in mediating the effects of ELA on the brain. Rodent intrauterine growth restriction (FR) is associated with lower and delayed levels of dopamine release in the Nucleus accumbens (NAcc) but this effect was completely abolished after insulin administration. To study the sex-specific modulation of insulin on impulsivity after the exposure to prenatal adversity, we used a FR model in Sprague Dawley rats by applying 50% food restriction during pregnancy (day 10 onwards) and cross-fostering all animals to Ad libitum dams at birth. Adult impulsive behavior was evaluated using the delayed gratification task in males and females injected with saline or insulin (5IU/Kg.) IP 5 minutes before the test. Female FR rats are more intolerant to delayed rewards than Adlib females, while this effect is less prominent in males. Furthermore, insulin injection increases the tolerance to delay in FR females but has no effects in FR males. Our results indicate that there is a neuroendocrine sex-dependent modulation of impulsivity through the insulin pathway, possibly acting on the dopaminergic system involved in impulsivity control. This work contributes on the understanding of the role of metabolic signals modulating the effects of early life environmental conditions on neurodevelopment.

P2-E-427: Time your dopamine? Is the habenula the pacemaker for nigrostriatal dopaminergic oscillations?

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Dopamine, a central messenger in the brain, plays a role in regulating behaviours including reward, learning, and motor control. Alterations to the dopaminergic system has been associated with various disorders - such as addiction, schizophrenia, and Parkinson's. The habenula is uniquely positioned to act on a large source of dopaminergic neurons, sending signals to the ventral tegmental area (VTA) and the substantia nigra (SN). We are investigating the habenula as a principal pacemaker for the production and release of dopamine along the nigrostriatal pathway. Using male and female Bmal1 floxed mice, we injected AAV-2/9 Cre-eGFP virus into the habenula to selectively knockout Bmal1. In a previous

experiment, mice underwent a battery of behavioural tests where we found a motor phenotype, with a significant impact on motor coordination in both male and female knockout mice. Daily rhythms of gene expression, primarily targeting the circadian clockwork and cell signalling pathways, were also assessed. Results indicate changes in molecular processes in the dorsal striatum (DS) and SN of knockout animals, that may contribute to the observed behavioral phenotype. Causal to this could be alterations in dopamine levels in the DS over the 24-h day, as indicated by preliminary results using liquid chromatography coupled mass spectrometry (LCMS). As proper functioning of the nigrostriatal pathway is presumably maintained by a mutual interaction of the circadian clock and dopaminergic system, these findings support that the habenular clock is a critical component in this relationship.

P2-E-428: A role for adipose triglyceride lipase (ATGL) in microglial inflammation and anxiety-like behaviour

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Lipid droplets (LD) accumulate within microglia during pro-inflammatory activation, in a similar manner to that seen in macrophages. LDs act as stores of neutral lipids, and as sites of eicosanoid synthesis. Loss of adipose triglyceride lipase (ATGL), the enzyme which catalyses hydrolysis of stored triglycerides, reduces inflammation in macrophages, suggesting an active role for LD dynamics in cellular inflammatory signaling mechanisms. Taking these data together, we hypothesized that loss of ATGL activity from microglia reduces neuroinflammation, and prevents the associated anxiety-like behaviours. Mouse primary microglia treated with Atglistatin and/or lipopolysaccharide (LPS) were used to assess the role of ATGL on lipid droplet accumulation and inflammatory gene expression. A novel mouse model with specific loss of ATGL from microglia (CxCR3-CreER/ATGLlox/lox) was used to study the role of microglial ATGL on inflammation in vivo. To model neuroinflammation, animals were administered with LPS. Inflammation reduced expression of ATGL and increased accumulation of LDs in vitro. Inhibition of ATGL activity in vitro and specific loss of ATGL expression from microglia in vivo reduced gene expression of pro-inflammatory cytokines in response to LPS treatment. In vitro, protein expression of pro-inflammatory cytokines was also reduced. Loss of ATGL increases body weight during ad libitum HFD compared to control animals, without affecting food intake. ATGL-KO reduced anxiety-like behavior in light-dark box testing, compared to ATGL expressing controls after LPS treatment. Together these data suggest reduced neuroinflammation and anxiety-like behaviour in animals lacking microglial ATGL.

2-E-429: Role of astrocytic glucocorticoid receptor signaling in the adaptive response to metabolic stress

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Glucocorticoid receptor (GR) activation in the brain strongly influences energy homeostasis and behaviour. Indeed, disruption of this dynamic neuroendocrine response contributes to the development of metabolic disorders and behavioural deficits. Despite these data, little is known about the cellular effectors of adaptation to metabolic stress. Considering recent evidence suggesting an important role of astrocytic GR activity in regulating the synaptic adaptations to swim stress, we questioned whether astrocytes are involved in adaptive responses to metabolic challenges (e.g. fasting). Therefore, we set out to test the hypothesis that astrocytic GR signalling regulates physiological adaptations to metabolic stress. We generated transgenic mice lacking GR in astrocytes crossing Glast-CreERT with GRflox mice. Under basal conditions, body weight and fat mass are significantly higher in astrocyte GR KO male mice, which move less than controls. This phenotype was absent in females, suggesting distinct roles of astrocyte GR signalling between sexes. In response to a 16h fast (acute stress), we observed a reduction in body weight, that did not return to baseline levels in astrocyte GR KO mice. This is combined with increased energy expenditure during fasting and higher glucose utilization during refeeding. This blunted response to fasting was associated with an absence of characteristic CORT response to fasting. Together, these results suggest that astrocytic GR signalling regulates body mass and composition, highlighting astrocytes' crucial role in adaptation to metabolic stress.

P2-E-430: Sleep deprivation activates basolateral amygdala neurons

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Sleep deprivation (SD) is associated with worsened physiological and mental health. To develop interventions against SD-related deficits, we must identify brain regions compromised by sleep loss. Preliminary findings from in-house whole brain tissue clearing indicated that the amygdala is activated following SD. However, the specific SD-activated amygdalar nuclei and their electrical properties were unresolved. We parcellated amygdalar nuclei using Nissl-stained coronal sections and generated standardized brain maps using Allen Reference Atlas templates to delineate cFOS+ amygdala cells in male wildtype mice that underwent either 4 h SD, 4 h SD with 2 h recovery sleep (RS), or slept undisturbed (control group). There were significantly more cFOS+ cells in select amygdalar nuclei after SD, including the basolateral amygdala (BLA). Interestingly, the number of BLA cFOS+ cells remained elevated after RS. To assess if increased cFOS expression corresponded with functional neuronal activation, we performed whole-cell patch-clamp recordings from acute amygdala slices of control and SD mice. SD-BLA cells were more excitable and received more excitatory input. In aggregate, we show that increased cFOS expression corresponded with SD-mediated cellular excitation within the BLA. Ongoing studies will employ excitatory and inhibitory chemogenic receptors in the BLA of inducible Fos-cre mice to determine if SD-activated BLA cells are engaged by heightened arousal or mounting sleep pressure during SD. These amygdalar outcomes may also be linked to SD-related emotion and mood deficits.

P2-E-431: Neural signature of CRH-PVN neurons during innate escape

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Selecting the optimal defensive strategy in response to threats is critical for survival. This complex decision process is governed by multiple brain regions and can be influenced by both external and internal factors. Advancing aerial predators trigger escape behavior that relies on recruitment of several key nuclei. CRHPVN neurons show an increase in activity in response to the visual threat that anticipates escape initiation. We have previously shown that uncontrollable stress decreases escape behavior by reducing CRHPVN anticipatory activity in response to a looming, advancing predator. Similarly, optogenetic inhibition of CRHPVN neurons prior to presentation of the visual stimulus decreases escape, indicating a key role for these cells in escape initiation. Here we sought to better understand the activity signatures of individual CRHPVN neurons during escape initiation. We used head-mounted miniscopes in freely moving animals to evaluate single cell calcium activity during the behavioral task. We focused on two different time points, prior to and during presentation of the visual stimulus to assess changes in cell activity in response to the stimulus. This analysis showed that the activity of the cell before the stimulus determines the probability of the same cell to be recruited during the response to a visual threat. Also, higher population activity pre-stimulus decreases the probability of new cells being recruited and as a result the probability to escape is reduced. In contrast, a quieter network is observed before the trials that resulted in an escape outcome. We also asked whether the escape decision is governed by a hard-wired network of cells and probed the requirement for the time-specific cell activity in the execution of the proper behavioural outcome.

P2-E-432: LPS-induced neuroinflammation promotes homeostatic disorders in mice

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Chronic neuroinflammation is a biological phenomenon with multiples sources, which can in turn provoke or aggravate many pathologies such as cognitive decline or neurodegenerative disorders. An important characteristic of neuroinflammation is its persistence; while peripheral inflammation can rapidly be resolved after a viral or bacterial infection, for example, neuroinflammation can become chronic and last for years, or even become permanent. The aging western population, environmental pollutants, and the SARS-COV2 pandemic form together a deleterious cocktail that will likely lead to increased prevalence of persistent neuroinflammation in the population. While metabolic disorders such as obesity are known to themselves generate neuroinflammation, little is known if, in opposite, chronic neuroinflammation in a normal-weight individual can sensitize to weight gain. This project aims to understand if the presence of neuroinflammation can modulate limbic and hypothalamic networks to facilitate the development of metabolic disorders. Using a mouse model of LPS-induced neuroinflammation, we observed changes in energy metabolism upon exposure to high-fat diet. We

further examined relevant circuitries, and whether cognitive and anxio-depressive behaviors are affected.

2-E-433: Characterizing recurrent inhibitory circuits of corticotropin-releasing hormone neurons in the hypothalamus

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Introduction: Corticotropin-releasing hormone (CRH) neurons of the hypothalamic paraventricular (PVN) nucleus are crucial in regulating the body's neuroendocrine stress response. We recently showed that in vivo firing activities of PVN-CRH neurons in mice rapidly and reversibly transition between two distinct activity states. Our computational model predicted that recurrent feedback inhibition between PVN-CRH and GABAergic neurons could control the activity-state switch. However, the neuroanatomical and neurochemical identities of these predicted GABAergic neurons remain undetermined. Methods: To examine GABAergic neurons that form recurrent connectivity with PVN-CRH neurons, we used a combination of retrograde neural tracing and anterograde functional connectivity mapping. Briefly, we retrogradely labelled PVN-projecting GABAergic neurons and anterogradely expressed an excitatory opsin in PVN-CRH neurons. In acute slices, we made whole-cell patch-clamp recordings from the PVN-projecting GABAergic neurons and optogenetically stimulated the soma and axons of PVN-CRH neurons. Results: Our results implicated two candidate brain areas where PVN-projecting GABAergic neurons receive functional inputs from PVN-CRH neurons. Interestingly, in these GABAergic neurons, PVN-CRH neurons form both fast (glutamatergic) and slow (non-ionotropic) synaptic transmission. We will further characterize the synaptic properties underlying the recurrent inhibition and neurochemical identities of these GABAergic neurons. Our experimental data will then be used further to refine the current computational circuit models for PVN-CRH neurons.

P2-F-434: Orbitofrontal brain regions underpin the effect of closed-loop auditory stimulation in sleep: a MEG study

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Closed-loop auditory stimulation (CLAS) is a technique in which sounds are timed to interact with endogenous brain activity. CLAS of slow oscillation up-states in sleep is becoming a popular tool to study sleep's functions, as it can increase slow oscillations, evoke sleep spindles, and enhance memory consolidation of certain tasks. However, few studies have examined the specific neurophysiological mechanisms involved in CLAS, in part because of practical limitations to commonly used tools. To evaluate evidence for possible models of how CLAS might generate slow oscillations, we simultaneously recorded electro- and magnetoencephalography in six healthy young participants who received auditory stimulation across sleep stages. The results suggest that auditory information reaches ventral frontal lobe areas via non-lemniscal pathways. From there, a slow oscillation is created and propagated. We demonstrate that while the state of excitability of tissue in auditory cortex and frontal ventral regions

shows some synchrony with the EEG-recorded up-states, it is the state of ventral frontal regions that is most critical for slow oscillation generation. Our findings advance models of how CLAS leads to enhancement of slow oscillations, sleep spindles, and associated cognitive benefits, and offer insight into how the effectiveness of brain stimulation techniques can be improved.

P2-F-435: Sleep spindle closed-loop auditory stimulation efficacy on memory consolidation in older adults

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Closed-Loop Auditory Stimulation (CLAS) of slow-oscillations up-states in sleep elicits additional SOs, and enhances memory consolidation. Stimulating SOs also induces sleep spindles, which are transient bursts of brain activity in the sigma frequency range (~11-16 Hz) observed during NREM2 and NREM3 sleep. However, targeted CLAS of sleep spindle up-states is more technically challenging due to their shorter duration and higher frequency range. To address this issue, we developed a device, the Portiloop, which is capable of real-time detection and stimulation of endogenous sleep spindles. We used the Portiloop to stimulate spindles in the sleep period following learning, and compared the physiological and behavioral effects of spindle stimulation between younger and older adults. Forty younger (18-40) and 10 older (60-75) healthy adults were divided between unstimulated sleep and spindle stimulation condition. While sleeping, EEG activity was monitored and participants were stimulated with sound. Participants learned and were tested pre- and post-sleep on three randomly ordered cognitive tasks assessing declarative (Grid-Location), procedural (Motor Sequence Learning), and complex auditory-motor memory (piano-learning, used as an ecologically valid measure of integrated memory). We will evaluate the effectiveness of stimulating sleep spindles on different types of memory across aging groups. Our work aims to further explore the role of sleep spindles in memory consolidation, towards more effective CLAS, and potential interventions.

P2-F-436: Measuring cognitive load across tasks with portable sensors

Measuring cognitive load across tasks with portable sensors Anita Paas[1], Giovanni Beltrame[1], David St-Onge[2], Emily Coffey[1]
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Cognitive load (i.e., the mental capacity it takes to perform a task) is an important factor of human performance. Performance is negatively affected when cognitive load is too high (overload) or too low (underload), leading to decreased efficiency and productivity, increased errors and fatigue and stress on the operator. Accurately monitoring cognitive load during performance is of growing interest in real-world applications (i.e., in industry, medicine, disaster relief, transportation, and exploration), as workload measurements can be used to adapt task demands or automation levels so as to maintain optimal operator performance and improve safety. Our research goals are to investigate the effectiveness of portable physiological sensors to measure cognitive load and to test if physiological responses to cognitive load are generalizable across simple and complex tasks. We record neural activity

(EEG), pupil diameter, skin conductance, and heart rate variability as people perform simple and complex tasks with different difficulty levels. We expect that EEG alone will provide the most accurate measurement of cognitive load across both simple and complex tasks, but that a combination of sensors will provide increased accuracy in measuring cognitive load across tasks, and that workload level in each task will generate similar physiological responses. The results of this research will form the basis for upcoming experiments in virtual reality and in the field and provide a set of portable physiological measures that can be used to predict cognitive load in diverse applications.

P2-F-437: Speeding up subjective time with optogenetic modulation of nigrostriatal dopamine function

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Dopaminergic function is implicated in the perception of event durations in the seconds-to-minute range. For instance, the dopamine clock hypothesis attributed the role of clock ticks to nigrostriatal dopamine signaling, while the striatal beat frequency model implicates both mesocortical and nigrostriatal dopamine in modulating cortical oscillation-based coding and learning of time intervals, respectively. We investigated the effect of the inhibition of substantia nigra pars compacta (SNc) dopamine neurons in Tyrosine-Hydroxylase Cre (Th-cre) mice on timing behavior. We trained 13 Th-cre male mice on the differential reinforcement of response duration (DRRD) with 3-sec target interval, which required mice to depress lever at least for 3-sec to receive reward. Two groups of mice were injected with either inhibition (AAV-EF1a-DIO-eNpHR3.0-mCherry) or control (AAV-EF1a-DIO-mCherry) viruses into SNc for optogenetic manipulation. Temporal production of mice in the inhibition group was shorter and their variability were higher in trials with optogenetic stimulation compared to no stimulation trials. The control group did not exhibit any of these effects of optogenetic stimulation. Diffusion decision theoretic analyses of the data suggested that inhibition of SNc decreased the decision threshold and increased the rate of temporal integration. These results suggest that inhibition of dopaminergic activity in SNc speeds up the internal clock and leds to less cautious decision biases.

P2-F-438: Rewarding value or prediction error: settling the debate over the role of dopamine in reward learning

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The discovery that DA transients can be mapped onto the reward prediction errors in temporal difference models is a pinnacle achievement of neuroscience. Yet, there is abundant evidence that DA activity reinforces actions, suggesting it serves as an intrinsically rewarding event. These two possibilities are so conceptually intertwined that it is not surprising that they have been so far experimentally conflated. Here, using computational modeling, behavioural blocking and optogenetics, we show that stimulating VTA DA neurons promotes learning even when a natural reward and DA stimulation are held

constant across the learning phases of blocking. These findings provide strong evidence in favour of the prediction error hypothesis rather than encoding the rewarding value of appetitive events.

P2-F-439: Individual recognition of familiar conspecifics in C57BL/6 mice

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Social memory, or the ability to recognize individuals, is critical to the survival of social animals. Rodent social memory tests are commonly based on novelty where recognition is determined by the subject's preference to interact with a novel, rather than a familiar, target. However, this method depends on the categorical recognition of novelty and not individual recognition. We developed a paradigm to test individual recognition for two familiar social targets using C57BL/6 mice. Subjects interacted with a neutral CD1 mouse and experienced attacks by an agonistic CD1 mouse. The following day a social discrimination test measured interaction times with both social targets and found that subjects spent less time interacting with the agonist compared with the neutral CD1. A decrease in interaction was not observed in control subjects that were not previously exposed to the CD1 targets or in trained subjects tested with social targets that were neutral and novel or both novel. We also modified a fear conditioning protocol by associating one of the two CD1s with footshocks and trained animals over 3 days. A social discrimination test revealed avoidance of the shock-associated CD1 only. These findings are the first to reveal individual recognition in mice. We have developed the first social memory task that calls for the recognition of two familiar targets and which is not rooted in the identification of novelty. Individual recognition tasks may be used to examine neural mechanisms of disorders with deficits in social recognition, such as autism spectrum disorder.

P2-F-440: The Effects of the Selective Deletion of STEP in the CA2 Hippocampal Region on Social Memory

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The CA2 region of the hippocampus plays a key role in the processing of social memory and to grasp a better understanding of the synaptic transmission underlying social memory, regulatory synaptic proteins such as STriatal-Enriched protein tyrosine Phosphatase (STEP) have been under scrutiny. The physiological role of STEP is to oppose synaptic strengthening that take places during synaptic plasticity. Thus, STEP needs to be degraded to enable the activation of cellular and molecular pathways important for plasticity processes. Since STEP has been shown to be strongly expressed in the CA2, the objective of the current study is to determine if the selective deletion of STEP in the CA2 area will affect the social memory in the rodent model. With the aid of CRISPR/CAS9, the expression of STEP phosphatase was suppressed specifically in the CA2 region, and then mice were evaluated in a battery of social behavioral tasks (social memory test, social interaction test, tube test, three chamber social interaction test) in conjunction with other forms of memory tests (Morris water maze, object recognition test, and passive avoidance test) to ensure that the effects on social memory could be distinguished from other forms of

learning and memory. At this point, we have confirmed the deletion of STEP in the CA2 with immunostaining, and we are in the process of collecting behavioral data to support our hypothesis. It is expected that the deletion of STEP will lead to social memory impairment without impacting other forms of learning and memory.

P2-F-441: View cells in macaque hippocampus and lateral prefrontal cortex during virtual navigation

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View cells, cells that are selectively activated by a particular view of an environment have been mainly described in the primate hippocampus (HPC). Here, we explore view selectivity in the HPC and the lateral prefrontal cortex (LPFC) of rhesus macaques performing a context-object association task while navigating a virtual environment via a joystick. We show that specific views containing task relevant objects elicit selectivity in a high proportion of HPC units, and an even higher proportion of LPFC units. We explore responses at different locations in the maze where animals select one of two objects. Place selectivity was scarce and generally dependent on view. Additionally, most view selective units were not affected by changing the object colour or the context cue, two task relevant parameters. However, the units that were selective for object colour or the context cue were generally also selective for view. Our results show that during navigation in a virtual environment with complex and dynamic visual stimuli, both the HPC and the LPFC contain a proportion of units selective for view. Thus, view selectivity is not exclusive of HPC neurons, but can also be found in high level association cortices like LPFC.

P2-F-442: Modulation of the anxiolytic effects of cis-resveratrol by cap-dependent translation

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Resveratrol (RSV) is a phenolic compound found in many plant and plant products, and it exists as cis (cis-RSV) and trans (trans-RSV) isoforms, with trans-RSV being the most abundant. Trans-RSV is enzymatically converted to cis-RSV, which may explain some divergent results in clinical trials evaluating cognition. RSV has also been proposed as a potential treatment for mood disorders. In animal models, RSV decreased immobility time in the forced swim test (FST), increased exploration of the center of the open field (OF) and open arms of the elevated plus maze. Recently it was shown that trans-RSV is neurotoxic, but cis-RSV is neuroprotective and increases de novo protein synthesis through the mammalian target of rapamycin 1 (mTORC1) pathway in cultured neurons, suggesting that the therapeutic effect is restricted to the cis isoform. We examined whether cis-RSV had behavioral effects consistent with antidepressant or anxiolytic treatments and whether these were dependent on mTORC1. Following 14 daily injections of cis-RSV (IP, 10 mg/kg) in mice, we found that males had increased exploration of the center of the OF compared to the saline treated group, without altering general locomotion. In contrast, females had a decrease in mobility and exploration of the center of the OF. The

effects on exploration of the center of the OF were absent in mice mutant for an mTORC1 effector on translation. cis-RSV did not affect immobility in the FST in any strain of male and female mice. These effects suggest a sex specific effect on measures linked to anxiety, that depend on mRNA translation.

P2-F-443: Long-term behavioural consequences of higher heroin intake in male and female rodents

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Opioid overdose-related death is a prevalent issue affecting Canadians around the nation. To better understand the problem, and specifically the underlying brain mechanisms, animal models for substance use and relapse are used. A body of literature focuses on the consequences of extended cocaine self-administration on abstinence and relapse in rats. Thus, the current research aimed to examine the behavioural effects and long-term consequences of higher heroin intake on the development of punishment-induced abstinence and stress-induced relapse. Twenty-four Long-Evans rats will be used as subjects (12 male and 12 female) for drug self-administration training. A new procedure is put forth that combines the long drug accessibility procedure and the seek-take procedure in order to examine these behaviours. Preliminary results show an increase in heroin intake due to longer drug availability, which may lead the rats to have a greater resistance to punishment during abstinence. Finally, it is expected that once subjects have reached abstinence, they will show higher relapse tendencies.

P2-F-444: The bidirectional effect of 2-AG on hyperdopaminergic states: implications for therapeutic 2-AG modulation in psychosis.

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The endocannabinoid system is dysregulated in schizophrenia (SCZ). Enzymes involved in the biotransformation of 2-arachidnoylglycerol (2-AG) are altered in SCZ; DAGL (2-AG synthesis) and MAGL (2-AG metabolism) are decreased in first episode psychosis/SCZ patients, and 2-AG is elevated in individuals at high risk of psychosis. In certain clinical contexts, elevation of 2-AG is desired. Thus, clinical trials of MAGL inhibitors (MAGLi) are underway; however, evidence suggests increasing 2-AG may be detrimental in SCZ. Before wide therapeutic use, it's imperative to understand the effect of MAGLi in vulnerable SCZ populations, and whether decreasing 2-AG is therapeutic. Therefore, we assessed pre-clinical effects of MAGLi (increase 2-AG) and DAGLi (decrease 2-AG) in models of hyperdopaminergia, based on well-established association between SCZ and increased subcortical dopamine. Dopamine transporter knockout mice (DATKO) exhibit subcortical hyperdopaminergia, exploratory hyperactivity, impaired sensorimotor gating, blunted response to psychostimulants, and disrupted lipid profiles. MAGLi exacerbated hyperlocomotion, sensorimotor deficits, and already disrupted lipid networks in DATKO. MAGLi increased reward association in DATKO, but not C57BL/6J wild type mice (WT), suggesting a worrisome addiction liability. Conversely, MAGLi exacerbated psychostimulant responses in both DATKO and WT. Data suggest that increasing 2-AG via MAGLi exacerbates states of hyperdopaminergia,

mediated by CB1. Interestingly, decreasing 2-AG (via DAGLi) presented opposite effects on all measured hyperdopaminergic behavioural outputs in both DATKO and WT. This highlights a potential therapeutic avenue for novel, dopamine-indirect treatments that target lowering 2-AG in vulnerable SCZ populations.

P2-F-445: Behavioural phenotypes in neurodevelopmental disorders

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Management of neurodevelopmental disorders (NDD) is complicated by diverse within-disorder presentations and a high degree of symptom overlap between disorders. Evidence suggests that current diagnostic criteria do not align well with behaviour or neuroanatomical metrics. Behaviour-based subgroups may facilitate studies examining biomarkers underlying clinical presentation. The objective of this study is to examine the link between gastrointestinal (GI) symptoms, immune medical history and behaviour in TD, autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) individuals. TD, ASD, and ADHD participants between 2-21 years of age were recruited through the Province of Ontario Neurodevelopmental Disorders Network (POND). Participants completed behaviour assessments measuring social communication, hyperactivity, inattention, anxiety, and repetitive behaviours. Data on GI symptoms and immune medical history were collected from a subset of participants. Using Gaussian mixture modelling, 1728 individuals were grouped into six clusters with distinct behavioural profiles. Five of the six clusters included TD and NDD individuals, while only one cluster was NDD-specific. Notably, this cluster exhibited high symptom severity across all metrics, and chi-square analysis shows a disproportionate burden of GI symptoms in the NDD-specific cluster ($p < 0.05$). Ongoing analysis will examine the association of immune medical history with behavioural clusters. The behavioural results support a diagnosis-agnostic approach to subgrouping individuals.

P2-F-446: Cortical dopamine D5 receptors regulate neuronal circuit oscillatory activity and memory in rats

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The dopamine D5 receptor (D5R) shows high expression in cortical regions, yet a role for the receptor in learning and memory remains poorly understood. This study evaluated the impact of prefrontal cortical (PFC) D5R knockdown in rats on learning and memory and assessed the role of the D5R in the regulation of neuronal oscillatory activity and glycogen synthase kinase-3 (GSK-3β), processes integral to cognitive function. Using an adeno-associated viral (AAV) vector, male rats were infused with shRNA to the D5R bilaterally into the PFC. Local field potential recordings were taken from freely moving animals and spectral power and coherence were evaluated in, and between, the PFC, orbitofrontal cortex (OFC), hippocampus (HIP), and thalamus. Animals were then assessed in object recognition, object location,

and object in place tasks. The activity of PFC GSK-3β, a downstream substrate of the D5R, was evaluated. AAV-mediated knockdown of the D5R in PFC induced learning and memory deficits. These changes were accompanied by elevations in PFC, OFC, and HIP theta spectral power and PFC-OFC coherence, reduced PFC-thalamus gamma coherence, and increased PFC GSK-3β activity. This work demonstrates a role for PFC D5Rs in the regulation of neuronal oscillatory activity and learning and memory. As elevated GSK-3β activity has been implicated in numerous disorders of cognitive dysfunction, this work also highlights the potential of the D5R as a novel therapeutic target via suppression of GSK-3β.

P2-F-447: Investigating emergent hippocampal dynamics through standardized high-throughput behavior and neuronal imaging using the McGill-Mouse-Miniscope (M3) platform

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Recent technical advances enable the recording of large neuronal populations during behavior resulting in increasingly complex datasets. We have established the McGill-Mouse-Miniscope platform to combine miniscope calcium imaging with standardized touchscreen-based behavioral testing. Our mission is to curate an open-source and standardized framework for acquiring, analyzing, and accessing high-quality data of the neuronal dynamics that underlie behavior and cognition throughout the brain in mice. Each experiment provides up to 1000 simultaneously recorded neurons from a single brain region over the course months as animals learn the task. To highlight the feasibility of this approach, we have collected hippocampal CA1 and CA3 recordings during the delayed trial-unique nonmatching-to-location (TUNL) task, which assess working memory and consist of an encoding phase, a delay phase and a retrieval phase. As expected, CA1 and CA3 neurons are spatially modulated, however, they also are sensitive to other behavioral features. We found that ~10% of neurons participate in sequences tiling the delay period, delay sequences are unique to the sample square location, and delay sequence cells are reliably activated during reward. We are now examining how this structure emerges in these regions during the initial learning of this task, and how network activity restructures when memory load is changed. These data will help to shed light on how large populations of hippocampal neurons encode a complex memory task and will allow for comparison across laboratories and mouse models.

P2-F-448: 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 and cell types, which receive and process inputs from many parts of the brain. However, 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 in vivo fibre photometry

to examine how reward-predicting cues are encoded by subregion specific circuits in the nucleus accumbens. We observe distinct patterns 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 distinct networks and locations within the nucleus accumbens.

P2-F-449: Effect of a lognormal spike-timing dependent plasticity rule on cell assembly capacity in spiking neural networks.

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Estimation of the storage capacity of the brain's neural circuits is one of the important neuroscience questions. It has been hypothesized that temporally coordinated neurons, or cell assemblies (CAs), represent mental or perceptual entities. Thus, evaluation of the number of CAs is key to answering this question. Previous modeling studies using a spiking neural network with axonal conduction delays and the add spike-timing dependent plasticity (add-STDP) have shown that many more CAs than that of Hopfield nets were detectable (Izhikevich,2006). However, one significant limitation of this study is the unrealistic, bimodal distribution of connection weights that result from the add-STDP rule. In the real brain, the synaptic connection weights are known to be distributed lognormally. Thus, we have implemented a lognormal spike-timing dependent plasticity rule (log-STDP, Gilson and Fukai, 2011) into a network of Izhikevich spiking neurons. First, we confirmed that a lognormal distribution of connection weights was in fact produced and maintained stably for a long simulation time of 24 hours. Next, like with real neural data analysis, we detected CAs in the Izhikevich nets by the method proposed by Russo and Durstewitz (2017). We found the log-STDP rule produced more CAs than the add-STDP rule. Interestingly, the number and size of the CAs produced by the log-STDP rule trended similar to those in the rat primary cortex. Taken together, our study suggests that the Izhikevich nets with the log-STDP rule provide a useful tool to investigate the brain's storage capacity.

P2-F-450: Neural and behavioural analyses of higher-order fear conditioning

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Memories about aversive events that elicit fear (i.e. first-order cues) can propagate across the memory network, linking fear to other stimuli (i.e. secondary cues, higher-order fear conditioning) experienced forward or backward in time. Second-order conditioning occurs when secondary cues are linked with first-order cues after the fear is experienced. In sensory preconditioning, memory linking occurs prior to the experience of fear. Here, we used these procedures in rats to examine the behavioral and neural processes that underlie this learning. We show that reduction in fear to the primary cues via repeated exposure in the absence of a fear-eliciting event transfers to sensory preconditioned but not to second-order fear memories. We used ¬c-Fos whole brain mapping approach to identify key neural substrates at the time of recall in both types of fear. Our neural analyses show a differential role for the lateral

orbitofrontal cortex (lOFC) in regulating fear to sensory preconditioned and second-order cues. Specifically, inactivation of the lOFC disrupted the former but enhanced the latter form of secondary fear. Further, the lOFC has dense and reciprocal projections with the basolateral amygdala (BLA) which has been strongly linked to fear encoding and expression. Silencing the lOFC->BLA pathway using DREADDs disrupted sensory preconditioned but not second-order fear. Silencing the BLA->lOFC pathway disrupted fear to both types of secondary cues. We investigated these BLA->lOFC populations in expressing sensory preconditioned and second-order fear using RNAscope in a within-subjects design. These findings are considered in terms of the content of learning that drives behavior.

P2-F-451: Reading the minds of others: self-generated eye gaze shifts are responded to faster than the computer-instructed ones

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Humans discern where others are looking quickly and spontaneously. It remains unknown however what underlying processes drive this important social process - directionality information of the eye gaze position or the mentalistic inference of a gazer's mind. To address this question, we asked participants to predict which location an actor was going to look at before they initiated the gaze shift. Critically, the actors' gaze shifts were either self-initiated or computer instructed, with participants unaware of this manipulation. Participants were reliably faster at predicting the location of gaze when the actors chose to look at a location compared to when they were instructed to look at a location. Thus, humans can reliably predict the location of self-generated gaze shifts in others. This suggests that gaze following critically includes a mentalistic component or the ability to 'read' the minds of others and does not solely rely on processing the directional information from the eye gaze position.

P2-F-452: Lapses of attention during encoding predicts subsequent spatial context memory and altered brain activity in medial prefrontal cortex

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Individuals vary widely in their ability to form episodic memories in rich spatial contextual detail. The ability to sustain attention during encoding may account for these differences. Yet, it remains unclear how trial-by-trial fluctuations in attention at encoding impact subsequent spatial context memory. In the present study, 38 healthy young adults (mean age = 26.5 ± 4.4, 21 females) completed the novel fMRI Attention at Encoding Task. Participants were instructed to encode colored photographs of common objects and their left/right spatial location. In addition, participants were asked to respond as quickly as possible to a central fixation cross that expanded in size at a random duration after each encoding trial. Response times (RTs) to the fixation cross preceding and following the object were hypothesized to reflect individuals' attention levels pre-stimulus and post-stimulus, respectively. Results indicated that slower post-stimulus RT, but not pre-stimulus RT, predicted poorer spatial context memory. This effect

was modulated by executive and attention-related factors. Furthermore, slower post-stimulus RT was related to reduced deactivation of the middle/superior frontal gyri at encoding, which was also negatively correlated with subsequent memory. Together, these findings advance our understanding about the impact of lapses of attention on associative spatial context memory, and its contribution to individual differences in episodic memory.

2-F-454: Orbitofrontal and hippocampal responses to hidden spatial goals

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Hippocampal place cells in rats generally distribute uniformly over neutral environments, but there is mixed evidence on whether they represent behaviorally-significant locations differently. For instance, reward-delivery locations often accumulate an increased density of place fields, while locations that rats must visit to trigger reward delivery elsewhere only sometimes show this effect. Here, we examined whether the spatial reward predictability of a location affected representations in hippocampus and orbitofrontal cortex (OFC), another brain region that frequently exhibits spatial tuning, as well as reward-related representations. Rats learned two unmarked goal locations in an open field arena. Pausing in either goal caused a food pellet to be delivered, but the goals differed in where the food was delivered. Pausing in the "fixed" goal dispensed a pellet to a consistent location while pausing in the "random" goal dispensed a pellet to an unpredictable location. Both goals were learned anew during each behavioral session. Over 94 sessions, we recorded 753 OFC units and 613 hippocampus units in 7 male rats. Of these, 82% of hippocampal units and 43% of OFC units showed spatially-specific firing. Spatial fields did not cluster around goal locations relative to non-goal locations, and approximately equal numbers of fields occurred near the fixed and random goals in both structures. These data suggests that place fields in the hippocampus and spatial fields in the OFC do not differentially represent goal locations based on their predictability of reward location.

P2-F-455: Reduced cage-lid hanging behaviour in mouse: the role of endogenous opioid, cannabinoid, and corticosteroid systems

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The translation of preclinical findings to humans in pain research is challenging. Our previous study (Zhang et al., 2021) showed that the depression of cage-lid hanging is a novel, translationally relevant pain outcome measure in mice. Stress contributes to psychiatric disorders like depression and anxiety. Under stress, the adrenal cortex secretes corticosterone in rodents. Chronic pain and depression frequently co-exist and exacerbate one another. This study aimed to assess the neuropharmacology of cage-lid hanging and its association with anxiety-depression states. Eighty-one male C57BL/6 mice (6-8 weeks - old) were used in this study. Mice were treated with drugs or vehicle. To investigate if opioidergic modulation participates in hanging behaviour, mice received morphine (1mg/Kg) or naloxone (3mg/Kg) IP, 30 minutes before assessing hanging behaviour. To determine whether endocannabinoid receptors

modulate it, mice were treated with AM251 (1mg/kg) in the same conditions. To investigate the effect of anhedonia on it, mice received corticosterone (35 µg/ml) in drinking water over four weeks and then were evaluated. Naloxone 3mg/kg and AM251 1mg/Kg statistically decreased hanging behaviour. Animals under corticosterone treatment displayed a significant increase in immobility in the forced swim test on week 4, compatible with depression states, and a significant decrease in hanging ($p<0.01$; 2way ANOVA + Bonferroni). These findings suggest that hanging behaviour is modulated by opioidergic and endocannabinoid signaling, and its depression seems to be related to anhedonia.

P2-F-456: Dorsal peduncular cortex activity influences anxiety-like behaviors in male and female mice.

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The medial prefrontal cortex (mPFC) is critical for attention, memory and decision making, but these functions can be significantly impacted by acute and chronic stress. The mPFC is comprised of several subfields, including anterior cingulate cortex (ACC), prelimbic cortex (PrL), infralimbic cortex (IL) and dorsal peduncular cortex (DP). While many studies have evaluated how the ACC, PrL and IL contribute to diverse mPFC functions, the DP has been historically understudied. Recent studies suggest that the ventral mPFC, which includes the DP, contributes to emotion regulation through its connections with subcortical structures such as the amygdala and thalamus. However, the specific contributions of the DP in regulating stress and affective behaviours remains unclear. In the present study, we injected Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in the DP to evaluate anxiety-like behaviours, cognition and stress responses in naïve male and female C57BL/6J mice. We found that chemogenetic excitation of the DP increased anxiety-like behaviours in the open field test, elevated plus maze and tail suspension test, but had no effect on behaviour in the forced swim test. Moreover, chemogenetic excitation of the DP increased c-Fos expression in the DP and significantly increased serum corticosterone measurements. In contrast, chemogenetic inhibition of the DP slightly improved auditory fear learning but had no effect on memory. Taken together, these results suggest that the DP can influence stress circuits and anxiety-like behaviours in male and female mice.

P2-F-457: Investigating the long-term evolution of retrosplenial cortex neuronal activity around hippocampal ripples

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The activity of neurons, both at individual cells and populations level, undergoes evolution over time even if its associated external variables stay stable. This evolution has been proposed to mediate memory consolidation by facilitating the incorporation of new information into the corpus of previously stored knowledge in the neocortex. Memory consolidation is thought to involve continual interactions between the hippocampus and neocortex during brain offline states when hippocampal ripples occur. Ripples are transient, high-frequency oscillations in the local field potentials (LFPs) recorded from the CA1 subfield of the hippocampus, during which the hippocampal-neocortical interactions are enhanced.

Therefore, it is of significance to the field of learning and memory to investigate the long-term evolution of peri-ripple neuronal activity in the neocortex. Such investigations may provide insight into the mechanisms by which neocortical neural networks contribute to memory consolidation which could have implications for treating dementia and Alzheimer's disease. With this in mind, we addressed the abovementioned question by recording the activity of the same population of pyramidal neurons from layers 2/3 of the agranular retrosplenial cortex (aRSC), an association cortex heavily implicated in memory processing, using two-photon calcium imaging across multiple days. Additionally, simultaneous recording of local field potentials in the hippocampus was conducted to detect ripples, enabling us to study the long-term evolution of peri-ripple neuronal activity in the aRSC.

P2-F-458: Differential requirements for retinoid signaling in aspects of memory processing

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The Vitamin A metabolite, retinoic acid, exerts both genomic and non-genomic effects in the developing and adult brain, effects which are mediated either through binding to retinoid receptors (RAR or RXR), or through direct interactions with other signalling molecules. In the adult vertebrate brain, deficient retinoid signalling can reduce hippocampal synaptic plasticity and thus detrimentally affect various types of learning and memory. Many effects of retinoids are conserved between species, and using both operant and classical conditioning paradigms, we have shown that retinoic acid also plays a key role in long-term memory formation in an invertebrate species. Whether retinoids affect other aspects of memory processing, such as reconsolidation and/or extinction have not yet been studied in vertebrates or invertebrates. Memory reconsolidation stabilizes an existing memory following its reactivation (during which time it enters a labile state and can be altered). Here, we provide evidence that retinoid signalling is required for memory reconsolidation following classical conditioning, though its requirement differs, depending on the number of training sessions and the dependency of reconsolidation on protein synthesis. We also provide evidence for a role of retinoid signalling in the process of memory extinction. These studies shed new light on the potential for retinoids to affect different aspects of memory processing in the adult brain.

P2-F-459: Age- and sex-dependent recruitment of the prefrontal-amygdala pathway in fear extinction

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Fear conditioning is a valuable tool in assessing emotional memory in animal models, resulting in an adaptive fear response that is critical for survival. Fear learning and extinction are developmentally regulated in humans and rodents. Specifically, rodents show two behavioural phenotypes of extinction: juveniles exhibit a permanent extinction that does not result in spontaneous recovery of the fear response (immature-type extinction), whereas in adults fear responses tend to re-emerge spontaneously following extinction training. The switch between immature- and adult-type extinction occurs around the juvenile stage in mice, and coincides with developmental changes in prefrontal-amygdala synaptic

connectivity. While prefrontal cortex projections to the basolateral amygdala (BLA) play a well-established role in extinction learning, the precise timing and contribution of the prefrontal-BLA circuit to the extinction switch remains unknown. Here, we investigated the necessity of the infralimbic (IL) - BLA pathway in extinction during early life using optogenetics. Mice were trained to associate a tone with a foot-shock, followed by extinction training and spontaneous recovery a week later. Females, but not males, exhibited immature (persistent) extinction at P21, which switched to adult-type extinction by P25. Further, optogenetic inhibition of the IL-BLA pathway during extinction learning suppressed extinction retrieval in males but not P21 females, suggesting that IL-BLA recruitment drives the developmental onset of adult, relapse-prone extinction.

P2-F-460: Pavlovian conditioned odour memory in the Neurexin1+/- mouse model of autism spectrum disorder

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Neurexins (NRXNs) are presynaptic cell-adhesion molecules that bind with postsynaptic ligands to regulate synaptic development and function. Altered Nrxn gene expression is linked to neurodevelopmental disorders, such as autism spectrum disorder (ASD), in which learning and memory are impaired. The Nrxn1+/- transgenic mouse model, with the loss of one Nrxn1 allele, is a novel model of ASD. Male and female Nrxn1+/- and WT (Nrxn1+/+; C57BL/6J) mice at 90-120 days of age were conditioned to dig in an odor pot to receive a sugar reward over 8 trials in a 1-day Pavlovian conditioning protocol. Their short- and long-term olfactory memory was compared with that of naïve mice receiving no odour conditioning. Using the time spent digging in the odour pot as a measure of olfactory memory, we hypothesised that Nrxn1+/- mice would have impaired long-term memory, however, they did not differ from the WT mice during the training day nor during 24-hour or 7-day memory tests. The Pavlovian conditioned mice, however, showed significantly more digging in the odour pot than naïve mice during both the learning and memory trials, indicating that digging behaviour accurately reflects olfactory learning and memory in this task. Overall, the results indicate that Nrxn1+/- mice do not exhibit impaired olfactory learning or memory based on this 1-day Pavlovian conditioning odour paradigm.

P2-F-461: Dopamine modulation of morphine drug discrimination in male and female rats.

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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 aimed 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. Flupenthixol and apomorphine inhibited sucrose seeking on test trials in all rats, likely through distinct mechanisms. Conclusion: Our findings lend support to a mechanism of OS involving gating of CS-induced dopamine release by FP or FN drug states.

P2-F-462: Evaluating theoretical models of hippocampal mapping across protracted experience.

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Survival requires that agents learn useful representations to navigate space effectively, including responses to dynamic changes in environments across experience. The hippocampus is known to have an important role in representing the environment, and disruption to hippocampal circuits severely impairs navigational abilities. Such results have stimulated the development of numerous models on cognitive mapping in the hippocampus and its role in cognition and behaviour. Importantly, such models make distinct but often overlapping claims about cognitive maps. Until now, there has been no consensus on how to compare such model-based predictions to empirical observation and adjudicate between competing views. In the present study, we conducted a series of systematic geometric manipulations of a large open arena while tracking activity in large neural populations in hippocampal area CA1 across protracted experience in freely behaving mice with single-photon calcium imaging. We show that repeated geometric deformations of environments produce robust changes to neural representation in CA1, and that greater network-level organization develops with experience. Next, we generate predictions from theoretical models on hippocampal mapping and compare our empirical observations to model-based predictions using representational similarity analysis (RSA). With this approach, we demonstrate that specific models show measurable improvements in predicting representational structure in CA1 population activity and its response to systematic deformations of environmental geometry and topology. Our findings thus support the use of such datasets to benchmark theoretical developments and demonstrate the utility of this approach to perform model-based comparisons.

P2-F-464: Age-Dependent Changes in Spatial Memory in 5xFAD Mouse Model of Familial Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by age-related memory deficits, cognitive decline, and neuropathology. The 5xFAD mouse line is a model of familial AD that exhibits behavioural deficits in spatial memory and neuropathology, including neurodegeneration, axonopathy, and amyloid beta

aggregation. The mammillary bodies (MB) and subiculum (Sub) are particularly susceptible to pathological changes in 5xFAD animals early on and input from the Sub to the MB play a role in integrating spatial information. Thus, the present investigation aimed to characterize age-dependent spatial memory deficits in the 5xFAD mouse model. Both transgenic and wild-type mice were tested at 3 and 5 months using a path integration spatial navigation task (testing the use of egocentric cues) and a cued conflict spatial navigation task (testing the conflict between egocentric and allocentric cues) on the Barnes maze. The path integration task required the mice escape to a familiar shelter in the dark by relying on their sense of body position relative to the shelter's known location. The cued conflict task introduced an visual LED cue to indicate the shelter location. During a subset of escape trials, the cue was shifted to a different position, creating a conflict between the actual location (based on self-motion cues) and the LED-indicated location. Additionally, we quantified age-related changes in neuropathological markers in the MB and Sub at 3 and 5 months.

P2-F-465: Oscillatory correlates of memory task performance: The effect of item manipulability

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Certain object properties may render an item as more memorable than others. One such property is manipulability, or the extent to which an object can be interacted with using our hands. Here we investigate if manipulability of a stimulus modulates memory task performance on both a behavioural and neural level. In particular, we recorded electroencephalography (EEG) from a large sample of individuals (N = 53) during a visual stimuli item recognition memory task. All stimuli were rated as either high or low manipulability. Retrieval involved asking participants to judge if the presented stimuli was also presented at the encoding stage. Our data analysis focused on activity in the theta (3.5-7 Hz) and alpha (8-14 Hz) rhythms, both of which have been implicated in attentional and memory processes. Activity in the theta rhythm over the central region was greater for high manipulability stimuli at both encoding and retrieval. At the retrieval stage, participants were significantly slower when responding to new as opposed to old high manipulability stimuli, an effect not observed for low manipulability. New high manipulability items were accompanied by an increase in alpha activity while low manipulability items were accompanied by a decreased activity in the rhythm. Together, these behavioural and oscillatory findings provide further evidence that manipulability affects the processing of visual stimuli during memory tasks.

P2-F-466: Rapid effects of estrogens on learning and memory in the hippocampus of male mice

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Nearly every aspect of hippocampus function, including memory formation and consolidation, is influenced by estrogens. It is now known that this can happen very rapidly, too rapidly for it to be the

consequence of classical gene-transcription processes. Many recent studies have shed crucial light on the rapid estrogenic facilitation of hippocampus short-term memory in ovariectomized females. However, despite high levels of estrogen receptor expression and the potent estrogen 17β-estradiol (E2), much less is known about how estrogens rapidly influence hippocampus-depended memory in males. Therefore, the goal of this study is to investigate the rapid effects of dorsal hippocampal estrogens in male mice. In this study, we used three different learning paradigms that test social and non-social aspects of recognition memory and spatial memory to investigate the influence of E2 administered to the dorsal hippocampus of male mice. Castrated male CD1 mice were infused with either vehicle, 25 nM, 50 nM, 100 nM, or 150 nM of E2 into the dorsal hippocampus 15 minutes prior to social recognition and 25 minutes prior to object recognition or object placement learning. These paradigms were created to enable the study of enhancing effects on short-term memory within 40 minutes of E2 administration, allowing the examination of estrogens' rapid effects. Based on previous findings from females we expect E2 to enhance social and object recognition, as well as object placement, suggesting that the rapid effects of E2 may improve general learning and memory functions in the hippocampus of male mice.

P2-F-467: The basal ganglia as a neural marker of first onset internalizing disorder in high-risk youth

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While research has linked alterations in resting state functional connectivity and structure of the basal ganglia to internalizing disorders, little research has examined whether these alterations may be pre-morbid vulnerabilities. This study examined resting state functional connectivity and grey matter volume of basal ganglia nuclei as markers of risk for developing a first lifetime onset of a depressive or anxiety disorder in adolescents at high familial risk. Participants were adolescents with one parent with a history of internalizing disorders, but with no such history themselves. 119 youth completed structural MRI scans, and resting state fMRI scans, as well as the Mini International Neuropsychiatric Interview-Kid (MINI-Kid) and the Youth Self Report internalizing symptoms scale at baseline. The MINI-Kid was completed again at 9- or 18-month follow-up for 99 participants to assess onset on depressive or anxious disorders. Analyses consisted of a multiple regression model, controlling for sex, age, and baseline symptoms. Decreased connectivity between the left putamen and the cingulate gyrus (pFDR = .02) and between the left pallidum and the precentral gyrus (pFDR = .03) at baseline predicted first episode onsets at either follow-up. Decreased volume of the left putamen and pallidum additionally predicted first onsets of internalizing disorders, although not after controlling for baseline symptoms. Altered structure and function of these regions may represent a pre-morbid risk factor for developing a clinically significant onset of an internalizing disorder. Results may have implications for understanding the neural bases of internalizing disorders episodes and for early identification and prevention efforts.

P2-F-468: Neuronal Diversity and Intrinsic Membrane Properties Across Cortical Areas in the Non-Human Primate

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Higher-order mental representations underlying working memory function, are believed to arise in the primate granular prefrontal cortex (PFC) in the form of stimulus-selective persistent activity. In vivo extracellular recordings from behaving nonhuman primates (NHPs), such as macaca mulata, have shown that persistent firing is absent in early sensory areas such as the primary visual cortex. However, the mechanistic basis of persistent activity in primate LPFC circuitry remains speculative; partly due to a lack of understanding of cellular properties across the NHP cortex. The common marmoset is increasingly used as a model for human cognition. It does have a granular PFC and single-unit recordings showing persistent firing have recently been reported. In our international consortium (NeuroNex), we aim to characterize intrinsic membrane properties and morphology of cortical neurons from the LPFC and V1 of marmoset and macaque monkeys using patch clamp electrophysiology in acute brain slices, similar to the Allen Institute Cell Type Database. To date, we accumulated over 500 electrophysiological recordings including both pyramidal cells and interneurons. Furthermore, we obtained numerous cell fillings that provide us further insight into cell identity and cross-area differences. Some of these data can be browsed on the website 'PrimateDatabase.com', a publicly available collection of intracellular recordings and reconstructions of the morphology. Our data provide insight into the fabric of the primate neocortex and enable modeling studies of working memory using realistic single-neuron simulations.

P2-F-469: Elevated dopamine D1 neuron activity disengages feeding and self-stimulation behaviour

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Pathological feeding is characterized by long bouts of consumption. Unfortunately, the psychological and neural processes reflected in bout duration, and an approach to normalize this feature of disordered consummatory behaviour remain obscure. Here, we show that bout duration reflects the integration of positive and negative tastes. In energy-replete mice, the mean bout duration of saccharine solution (0.03, 0.3, and 3%) consumption follows an inverted-U; ascending with increased sweetness and decreasing as saccharine activates bitter taste receptors. Next, we examined the role of dopamine type-1 (D1) and type-2 (D2) neurons in regulating saccharine solution consumption. Pharmacologically (ip) elevating the activity of D1 (SKF82958; 0.25 mg/kg), but not D2 (Raclopride; 0.06 mg/kg), neurons reduced bout duration. Promisingly, a novel pharmacotherapy (MP-10) that elevates striatal D1 and D2 neuron activity reduced bout duration. Lastly, we argue that ventral striatal D1 neuron activity is a signature of behavioural disengagement. In a procedure wherein mice control the duration of optogenetic self-stimulation of ventral striatal dopamine inputs, mice performed shorter bouts of high-frequency self-stimulation (2.5, 10, 40Hz), which were further reduced by activating (SKF82958; 0.25 mg/kg) D1 neurons. In sum, bout duration reflects the integrated value of food as determined by taste. Pharmacotherapeutic interventions that elevate the activity of ventral striatal D1 neurons may normalize pathological feeding and treat disorders characterized by excessive behavioural engagement.

P2-F-470: 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 social network of mice, group members interact with each other, play, and fight to consolidate their social rank. The behavioral ability that each mouse exhibits to control stress determines its status in the colony. This project aims 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 a library of 2000 images to automatically detect individuals and identify group behavioral characteristics through a hybrid machine tracking system consisting of DeepLabCut with a new MouseTag algorithm, evaluated by cross validation and root-mean-square deviation. We segmented behavioral sub-categories such as positive, negative, and neutral interactions evaluated by accuracy, precision and recall on each behaviour. Overall, our results suggest that automatic detection and behavioral categorisation algorithm can identify and track every single mouse in a complex colony efficiently over prolonged periods of time to improve the study of social dynamics.

P2-F-471: Using temporal gradients to assess the capacity for degeneracy in the neurobiology of conditioned fear

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The basolateral amygdala complex (BLA) is a well-known and integral part of the neurocircuits that support Pavlovian fear conditioning to many sources of threat and aversion. Interestingly, however, robust fear memory can also occur in the absence of the BLA, indicating degeneracy in the neurobiology of Pavlovian conditioned fear. In the case of brain circuits, this occurs when different circuits (e.g., with and without the BLA) achieve the same function (e.g., supporting Pavlovian fear conditioning). These findings question the necessary role accorded to the BLA in Pavlovian conditioned fear, and suggest that memory can be degenerately encoded in the brain, thus conferring memory with greater flexibility and robustness. However, the conditions that enable degeneracy are largely unknown, and studies that observed degeneracy in fear memory often destroy or inactivate the entire BLA. Compared with more precise approaches that target specific engrams, whole BLA lesions and inactivations may underestimate the capacity for degeneracy in fear memory. While BLA lesions cause lasting memory deficits, it is unknown whether selective lesions of engram cells can be compensated for by the remaining BLA neurons. To address this question, we employed our fos-LacZ system for deleting highly-active neurons to selectively lesion engram cells following a memory test. We then assessed fear memory at three future time points (3, 7 or 14 days post-deletion) to determine whether loss of the fear engram caused persistent memory deficits. Consistent with earlier work (e.g., Maren et al., 1996), our results support

the idea that loss of the BLA engram causes lasting memory deficits, indicating that the mere passage of time may be insufficient to enable degeneracy in circuits involving the BLA.

P2-F-472: High extraversion is associated with lower entorhinal cortex volume in cognitively unimpaired older adults

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Extraversion, a personality trait characterized by the tendency toward being sociable, lively, enthusiastic, and assertive is linked to risk of Alzheimer's disease (AD), but the direction of this association is unclear. This may be attributable to failure to consider the contribution of cognition in studies of extraversion and AD risk, since correlations between extraversion and cognition are reported, and lower baseline cognition discretely increases AD risk. We examined the association between extraversion and entorhinal cortex (EC) volume, a brain region affected early in AD and which predicts conversion to AD, while accounting for impact of cognition, affective symptoms, and other personality traits in cognitively unimpaired (CU) older adults. 42 CU adults (age=71.1 years, 27 females) with normal neuropsychological test performance and no known neurological conditions or psychiatric disorders completed structural magnetic resonance imaging of the whole brain, Montreal Cognitive Assessment test, and standard neuropsychological measures of processing speed, reasoning, language and memory. Regression analyses, with P<.10 as significance threshold for β estimates, assessed extraversion as a predictor of bilateral EC volume. In univariable modelling, extraversion was a significant predictor of left EC volume (β=-7.94, p=.044), explaining 7.5% of its variability [F(1, 40)=4.32, p=.044], but not of right EC volume. Extraversion remained predictive of left EC volume (β=-2.65, p=.008) after considering the contribution of cognitive measures, demographic variables, other personality traits, and affective state. This finding converges with results indicating that extraversion is inversely linked to amygdala volume, another brain region vulnerable to AD.

P2-F-473: Optogentic modulation of VTA DA neurons regulates learning through aversive prediction error

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Learning depends on prediction error, which refers to the discrepancy between actual and expected outcomes. Prediction error can be effectively illustrated utilizing a Kamin blocking paradigm. When a strong predictor of an outcome is present, the learned association between a novel cue and outcome is hindered due to minimal prediction error as the outcome is already predicted. Dopamine activity in the Ventral Tegmental Area (VTA) has been linked to reward prediction error, but its involvement in fear is not well understood. To address this, we employed an aversive blocking paradigm in both males and females and utilized optogenetics to manipulate VTA dopamine neurons and its transients in the nucleus accumbens and the basolateral amygdala. Our findings show that activating dopamine neurons in the VTA during expected shock in a blocking paradigm attenuated the blocking effect. Conversely, inhibiting

VTA dopamine neurons during shock onset mirrored an unblocking effect, thereby facilitating learning of an otherwise redundant cue and the outcome. These results provide causal evidence for the role of VTA DA in aversive prediction error and contribute to a greater understanding of the mechanisms involved. Taken together with the current body of research, we propose a valence-specific mechanism of VTA dopamine in coding fear and reward prediction error.

P2-F-474: Cell assemblies associated with rats' skilled reaching reactivate during slow-wave sleep

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Explicit and implicit memories are hypothesized to be represented by groups of neurons called cell assemblies (CAs). Previous studies show that CAs for explicit memory are primarily reactivated during slow wave sleep (SWS), however, reactivation of implicit memory is less understood. We analyzed neural ensemble activity in the primary motor cortex during behaviour and rest from four rats that were trained with a skilled single-pellet reaching task (Eckert et.al 2020). Using a CA detection method proposed by Russo and Durstewitz (2017), we detected a median of 13.94 CAs per recorded neuron over the bin sizes from 3-100 msec. The relative percentage and the size of CAs increased with increasing bin size, and there were significantly more synchronous CAs than sequential CAs. We also found that CA activation around rats' reaching behaviour could be clustered into four categories: pre-reach activation, reach activation, reach inactivation, and post-reach activation. Reactivation analysis showed that the CAs in the first three categories were reactivated in SWS but not in rapid eye movement (REM) sleep. There was also significantly more CA activation during spindles associated with slow oscillations (SOs) than spindles alone. Interestingly, these results are different from the principal component (PC) activation in pre-task REM, reported in Eckert et al. (2020). In summary, our study suggests that implicit memory may have multiple representations, e.g., CAs and PCs, which provides an important insight into reactivation of implicit memory.

P2-F-475: Pattern separation is impaired by activation of Gi-signaling in or pharmacological knockdown of dentate gyrus astrocytes and is restored with D-serine

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Keeping similar memories distinct from one another is essential to accurate memory retrieval. This separation is thought to be achieved via the process of pattern separation, by which distinct neural outputs are created from similar or overlapping inputs. Pattern separation is dependent upon adult-born neurons in the dentate gyrus (DG) of the hippocampus. Recent evidence suggests that astrocytes interact with adult-born neurons and are necessary for their integration into hippocampal circuitry. However, the role of astrocytes in pattern separation remains unknown. Here, we used two techniques to alter DG astrocyte activity. We employed Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to selectively activate Gi signaling in DG astrocytes of GLAST- and Aldh1l1-CreERT2 mice

performing a Spontaneous Location Recognition task. Gi activation by intra-DG administration of clozapine N-oxide (CNO) in DREADD-expressing mice impaired pattern separation, indicated by an inability to discriminate similar object locations. Next, we knocked down astrocytes in the DG via intra-DG L-α-aminoadipate (L-AAA) administration, which resulted in impaired pattern separation. Following this, intra-DG or systemic treatment with D-serine (NMDAR co-agonist) improved pattern separation. Finally, low doses of D-serine restored pattern separation in mice impaired by astrocyte Gi activation or L-AAA-induced knockdown. Collectively, these data suggest normal astrocyte functioning in the DG is required for pattern separation and may involve modulation of D-serine release.

P2-F-476: White matter correlates of episodic memory at midlife in females: Assessing the impact of menopause

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The brain's white matter tracts support the efficient transmission of information across brain regions necessary for cognitive operations, including episodic memory. Intriguingly, there is evidence that some females experience episodic memory decline during menopause. Yet, little is known about the impact of menopause on white matter and, crucially, the implications for episodic memory function at midlife in females. To address this, we used multivariate partial least squares (PLS) to examine the association between white matter microstructure (fractional anisotropy [FA], mean diffusivity [MD]) and episodic memory in a cohort of middle-aged females at different stages of menopause (pre-, peri-, post-menopause), as determined by the STRAW+10 criteria. Diffusion MRI scans (single-shell) and episodic memory task data were collected. The memory task assessed face-location associations and included "easy" and "hard" variants. PLS analyses identified a pattern of white matter microstructure that was differentially associated with task performance in peri- and post-menopausal females. Across implicated tracts, FA (but not MD) was positively associated with retrieval accuracy during the hard task in peri-menopausal females, and with retrieval accuracy during both hard and easy tasks in post-menopausal females. Although preliminary, our results are consistent with scaffolding theories of cognitive aging, and highlight the importance of considering chronological aging when studying cognition and brain function at menopause.

P2-F-477: Testing the interocular and surround suppression mechanisms in amblyopia

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Amblyopia is a neurodevelopmental disorder of vision. Individuals with amblyopia exhibit persistent spatial deficits in their amblyopic eye because of strong interocular suppression from the fellow eye. Our aim was to compare surround suppression mechanisms in amblyopia to determine whether the suppression is coming from the amblyopic eye itself or from the fellow eye. We employed a dichoptic center-surround masking paradigm. The psychophysical task was to detect the presence of a central target in a two interval-forced-choice procedure. Stimuli were horizontally oriented 0.5 cpd gratings. The

central test stimulus was 2 degrees and the surround mask 6.5 degrees in diameter. There were two interleaved test conditions: target presented to the amblyopic eye or to the fellow eye, and three surround mask conditions: no mask, fellow eye mask and amblyopic eye mask, giving a total of six conditions. We observed that contrast thresholds in the fellow eye were more elevated when the mask was also in the fellow eye (due to monocular suppression) than in the amblyopic eye. And amblyopic eye thresholds were raised in both the fellow and amblyopic eye masking conditions but to a larger extent in the fellow eye masking condition (due to dichoptic suppression). Overall, there is more dichoptic suppression in the amblyopic eye from fellow eye masks compared to suppression in the fellow eye from amblyopic eye masks. Moreover, amblyopes are susceptible to suppression irrespective of whether the suppression comes from the amblyopic eye itself or from the fellow eye.

P2-F-478: Social defeat stress in adulthood does not alter the Netrin-1/DCC system in the PFC of female mice

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Elevated levels of the Netrin-1 guidance cue receptor gene DCC in the adult prefrontal cortex (PFC) is a consistent trait of major depressive disorder in humans and plays a causal role in susceptibility to chronic social defeat stress (CSDS) in adult male mice. Although depression is twice more likely in women than men, the molecular mechanisms underlying this disparity remain unknown. Here we investigated if DCC receptors are dysregulated in the PFC of adult female mice following CSDS. Adult (P75±15) C57BL/6J female mice were exposed to CSDS for 5 minutes each day for 10 days. To induce aggression from CD1 mice, male urine was applied to females. Control mice were housed with a different conspecific every day. Following CSDS, mice were assessed in the social interaction test (SIT) and 24h later, PFC tissue was collected to measure Dcc mRNA expression. Defeated females were segregated into resilient and susceptible groups based on the SIT. Both susceptible and resilient mice showed a deficit in the nestlet shredding test, a measure of self-care-like behaviour. Compared to control mice, susceptible and resilient mice showed stress-induced increases in body weight. However, there was no group difference in PFC Dcc mRNA levels, in mRNA expression of Netrin-1 itself, nor in Unc5c - another predominant Netrin-1 receptor gene. These data indicate that contrary to males, CSDS in females does not alter the Netrin-1/DCC guidance cue system in the adult PFC 24 later, and that sexually dimorphic molecular process may mediate stress vulnerability. We are currently investigating stress-induced alterations in the PFC expression of microRNAs controlling guidance cues and changes in the Netrin-1/DCC guidance cue system in other brain regions in female mice.

P2-F-479: Components of Social Processes in Responses to Communication: Content Features, Affective Experience and Neural Responses

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Information sharing decisions shape outcomes across social, political, economic, and public health domains. Prior work has examined how features of content (e.g., particular words) and brain responses predict sharing. However, how these relate to core psychological processes in driving decisions to share remains unclear. We use appraisal theory as a framework to better understand how content features, brain responses, and affective experience together drive sharing, quantifying distinct and overlapping contributions of these three underlying components. Focusing on health-related messaging, we measured content features with text analysis, brain responses with neuroimaging (n = 41), and affective experience with subjective reports (n = 247), applying dimension reduction to map these features to a parsimonious set of underlying components. Results indicated that present-tense and emotion-related content features (adj R2 = 0.11, p = .018), brain responses related to reward (adj R2 = 0.16, p < .001), and experiences of information relevance and affective impact (adj R2 = 0.17, p = .001) were all predictive of article sharing. Moreover, when these three sets of predictors were combined, each provided incremental predictive validity, suggesting that they contribute unique information (overall adj R2 = 0.44, p < .001). Further analysis is underway for understanding the role of each component in mediating sharing. This work provides a framework, grounded in emotion theory, for understanding the interplay between content, brain, and affect, for population-level information sharing.

P2-F-480: Maternal gastrointestinal nematode infection positively influences development of hippocampal long-term potentiation consistent with enhanced long-term spatial memories in the uninfected juvenile mouse pup

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Infection of pregnant and lactating mice with the gastrointestinal (GI) nematode, Heligmosomoides bakeri, has been shown to up-regulate expression of genes critical for long-term potentiation (LTP) in the brain of 1 week old uninfected pups. Furthermore, 3-4 week old offspring of H. bakeri infected mothers were able to remember the location of an escape hole in the Barnes Maze Test after 7-days, while offspring of uninfected mothers could not, indicating enhanced long-term memory retention in response to maternal infection. The aim of the present study was to test the phenotypic consequences of this maternal nematode infection on hippocampal LTP in the uninfected juvenile offspring. Outbred CD-1 mice were infected repeatedly or sham infected during pregnancy and lactation. When offspring were 3 weeks old, we explored high frequency induced LTP in the hippocampal CA1 area using extracellular field recordings. LTP was observed in a higher proportion of pups of infected mothers (60%) compared to those of uninfected mothers (11%), indicating earlier onset of LTP in response to maternal infection. The low response of pups of uninfected mothers precluded us from detecting a significant difference in the intensity of the LTP signal. Taken together, these findings suggest that a maternal GI nematode infection positively influences offspring brain development, resulting in an earlier emergence of hippocampal LTP and the ability to retain long-term spatial memories.

P2-F-481: Therapeutic targeting of IL-10 signaling alleviates capillary stalling and cognitive impairment in Type 1 diabetes

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Type 1 diabetes (T1D) has been associated with impaired cognitive function and vascular pathology. However, whether T1D perturbs blood flow in capillaries and what mechanisms mediate this phenomenon, remain elusive. Here, we longitudinally imaged the cerebral microcirculation in the streptozotocin model of T1D. Imaging revealed an increase in the number of stalled capillaries in the somatosensory cortex of T1D mice. Stalled capillaries were primarily associated with RBCs rather than leukocytes. These in vivo findings were validated by i.v injection of microspheres, which indicated significantly higher levels of capillary obstructions in diabetic mice. Behaviourally, diabetic mice were not different from controls in tests of ambulatory activity and visual function. However, diabetic mice were significantly impaired in learning/memory tests. In order to provide a mechanistic explanation, we probed for multiple cytokines and found unusually high levels of IL-10 in diabetic blood plasma. We then manipulated the IL10RA receptors broadly or in a cell specific manner. We found that only the endothelial specific knockdown of IL10RA receptors reduced the number of obstructed capillaries in diabetic mice but not the neutrophil specific IL10RA receptor knockdown. To test a clinically relevant approach, we injected IL-10RA blocking antibodies and found this was highly effective in preventing stalled capillaries in diabetic mice. Furthermore, chronic treatment of diabetic mice with IL10RA blocking antibodies led to significant improvements in CBF and cognitive function. In conclusion, our data indicates that diabetes is associated with greater risk for capillary obstructions as well as learning/memory deficits and blocking the IL10Ra receptors could be a therapeutic approach.

P2-F-482: Compound 21 does not impair novel object recognition in long evans rats

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Novel DREADD agonists such as compound 21 (C21) are designed to be more specific with fewer off-target effects than the original agonist, clozapine-N-oxide, however evidence to support this claim is lacking. Thus, prior to employing DREADD manipulations it is critical to assess whether these agonists cause confounding effects in standard behavioural tests. Our lab sought to study whether C21 impairs novel object recognition in male (N=11) and female (N=12) Long Evan rats. Rats were tested 3 times and administered either saline or C21 (0.5mg/kg or 1mg/kg, i.p.). Twenty minutes post-injection, rats were allowed to explore two identical copies of an object (A, A) in a square testing arena for 5 minutes. After a 5 minute delay, rats were returned to the testing box and allowed to explore an identical, "familiar" copy of object A as well as a novel object (B) for 5 minutes. Time during the test phase spent exploring object B minus time exploring object A divided by their sum was used to determine a discrimination ratio (DR). Mean exploration times were not significantly different between sex or treatment in either sample or test phases. Rats generally spend more time exploring the novel, rather than the now familiar object during the test phase (female DR's saline: 0.4, 0.5mg/kg: 0.26; 1mg/kg: 0.25; male DR's saline: 0.46; 0.5mg/kg: 0.24; 1mg/kg: 0.43). DRs did not differ by sex or treatment. Given our results, C21 appears

suitable for use in future experiments using DREADDs to investigate the role of cortical subregions in novel object recognition and related behavioural tests.

P2-F-483: Long term effects of prenatal alcohol exposure on cognitive functioning in male and female rats: implications for brain aging and dementia risk

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Alzheimer's disease and other forms of dementia are a major public health concern. Prenatal alcohol exposure (PAE) has been shown to have negative effects on cognitive function and increase the risk for developing dementia. However, less is known about how the PAE-related cognitive deficits change as the individual ages. In the current study, we addressed this gap in the literature by evaluating the cognitive functioning of male and female animals as they age. Sprague Dawley pregnant rats were randomly assigned to: PAE - ad libitum liquid ethanol diet; or Control - ad libitum pelleted control diet. Their offspring were then subsequently tested in the Barnes maze at 6 months of age. The preliminary analysis of our results indicates that PAE females made more errors during the learning phase. During the reversal learning phase, PAE females made more errors during trial 3. In addition, during all phases females made more errors and took longer to locate their target escape holes, regardless of their condition. These initial findings suggest impaired spatial learning and memory in PAE females during learning and reversal learning phases at 6 months of age. However, these effects were not observed in PAE males suggesting that females may be more vulnerable to the effects of PAE. As this is a longitudinal study, the animals will be tested again at 12 and 18 months. This study will help us gain a better understanding of how PAE-related cognitive impairments may worsen with age, providing new insights into the potential link between PAE and the risk of developing dementia.

P2-F-484: Hippocampal CA1 VIP interneurons regulate encoding of episodic memory

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In the CA1 hippocampus, vasoactive intestinal polypeptide expressing interneurons (VIP-INs) make complex connectivity motifs by targeting GABAergic cells and pyramidal neurons (PYRs). The resulting inhibitory and disinhibitory circuit interactions can regulate memory encoding, but the specific role of VIP-INs in this process remains poorly understood. Here we combined in vivo calcium imaging and optogenetic manipulations using wireless tools in freely behaving mice to reveal the role of VIP-INs in encoding of episodic memory. First, consistent with previous studies conducted on head-restrained mice, we found that VIP-IN activity was modulated by animal locomotion. Second, VIP-INs increased their activity when animals entered a new environmental context. Third, the activity of these cells was significantly higher during the object exploration and increased even further in case of novel and spatially displaced objects. To explore whether the context- and object-dependent VIP-IN activity can

shape dynamics of PYR ensembles, we conducted in vivo calcium imaging of CA1 PYRs. Similar to VIP-INs, we found a consistent increase in PYRs' activity in response to novel context and object. Furthermore, object-specific optogenetic silencing of VIP-INs during encoding phase of the object memory task led to impaired object recognition memory, highlighting an important role of VIP-INs in memory encoding. Taken together, these data indicate that CA1 VIP-INs increase activity in response to changes in the environment and via circuit disinhibition may gate encoding of episodic memory and adaptive behaviors.

P2-F-485: Behavioural characterization of male and female offspring in a rat model of prenatal cannabis exposure

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The legalization of cannabis in Canada has changed the social narrative surrounding use and risk perception. Fetal developmental processes are sensitive to exogenous cannabinoids; thus, this study aims to investigate the effects of cannabis smoke exposure on offspring behaviour and provide a direct comparison between phytocannabinoid injection and smoke exposure. Pregnant rats (n=89) were treated daily between gestational days (GD) 6 and 20 with either high-THC smoke (17.83% THC), high-CBD smoke (12.98% CBD), 3 mg/kg i.p. THC, 10 mg/kg i.p. CBD and i.p vehicle or air control (Control). Animals were reared for behavioural analysis starting in adolescence (PND30-40). Dams treated with THC gained less weight than control dams ($p<0.0001$). Litters treated with i.p THC and CBD were (~25%) smaller than control litters and smoke treatments ($p=<0.0001$), with no effect on pup weights. For adolescent open field test (OFT), there was no interaction, but a main effect of treatment ($p=0.03$) and sex ($p=0.01$) on time spent in the center zone, where i.p THC males spent (~40%) more time in the center zone than controls, i.p CBD, and high-CBD smoke but not high-THC smoke males. For OFT total distance travelled, there was only an effect of sex ($p<0.0001$), where females moved 17% more than males. For social interaction, there was only an effect of sex ($p=0.0006$), where female pairs spent 10% less total time within 20cm than males. Further analysis is underway for EPM, MK-801 locomotor activity and social interaction. This model is the first to explore prenatal cannabis smoke exposure in adolescent rat offspring. These results support existing but limited knowledge on how different routes of administration may contribute to inconsistent behavioural phenotypes in offspring.

P2-F-486: Changes in dorsal premotor cortical activity during learning of a decision-making task

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Many neurophysiological studies have shown that while monkeys make decisions between different actions, the process of deliberation influences neural activity in sensorimotor regions, including dorsal premotor cortex (PMd), posterior parietal cortex, and even primary motor cortex. These findings have led to hypotheses suggesting that the brain decides between potential actions by representing them in parallel within sensorimotor areas, and then resolves the competition between them using information

about relevant biases such as expected value and effort. However, as in most neurophysiological studies, these observations were made in highly trained animals that learned and practiced their tasks for many months before recordings were conducted. It is therefore possible that the above conclusions only apply to overtrained animals in which executive control has become largely automatic, and raises the question of what happens when a monkey is learning a reach-decision task for the first time. To assess whether sensorimotor regions are also involved during learning, we recorded spiking activity of isolated neurons and local field potentials (LFPs) in PMd throughout a monkey's training in a reach decision task (the "tokens task"). We found that during even the earliest stages of learning, activity of individual neurons and LFPs clearly reflect not only the choice that is made, but also the sensory evidence leading to that choice. These results are consistent with the hypothesis that PMd is always involved in the process of deliberation about reaching actions.

P2-F-487: Impairment of olfactory fear extinction in aged rats parallels impaired NMDAR-LTD in the piriform cortex

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Extinction of fear memories allows animals and humans to adapt to their changing environment and is a measure of behavioural flexibility. Extinction mechanisms and their therapeutic implications for fear-related disorders have been studied extensively. However, how aging impacts extinction learning is not well understood. Using a rat model of odour fear extinction, we show that extinction of a learned odour fear memory was impaired in aged rats, paralleled by inducible ex vivo long-term depression (LTD) in the piriform cortex (PC). Young rats acquired odour extinction and LTD was not inducible following extinction training. These results suggest that extinction learning is associated with PC LTD, thus preventing further LTD induction ex vivo. We further show that extinction in young rats is mediated by NMDA receptors (NMDARs). NMDAR blockade via systemic injection of MK-801 or intra-PC APV before extinction training prevented extinction in young rats, and ex vivo NMDAR-dependent LTD became inducible. There is a developmental switch from NMDAR- to L-type calcium channel-dependent LTD in the PC during aging, which may interfere with odour fear extinction. By administrating the partial NMDAR agonist D-cycloserine in aged rats before extinction training, we successfully induced extinction of the odour fear memory in aged rats. Hence, the impairment in odor fear memory extinction in aged rats may relate to the hypofunctioning of NMDARs and impaired NMDAR-dependent LTD. Enhancing NMDAR function may improve learning and flexible behaviour in the aged population.

P2-F-488: Fecal microbiota transplantation from fibromyalgia patients causes pain in mice

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Fibromyalgia is a complex and chronic pain syndrome characterized by widespread pain, accompanied by fatigue, sleep disturbances and cognitive dysfunction. It is estimated to affect 2-8% of the general

population, primarily women. The etiology of fibromyalgia is unknown, and it is difficult to diagnose or treat. It has been shown that the gut bacterial community composition is altered in fibromyalgia patients compared with healthy donors, however, it is unclear whether these changes contribute to the disease pathophysiology. Here we show that transplantation of the gut microbiota from fibromyalgia patients to germ-free mice or antibiotics-treated mice results in pain hypersensitivity and reduced general activity. The tail suspension test showed that colonization also induced depression-like behaviour at chronic but not acute time points. Single-cell RNA sequencing of the peripheral blood mononuclear cells revealed significant alterations in gene expression in monocytes, B cells and other cell types. In addition, fibromyalgia microbiota altered bile acids metabolism and changed skin innervation in recipient mice. Spinal microglia were activated in the recipient mice and the depletion of microglia partially alleviated the development of pain hypersensitivity. Re-colonization of fibromyalgia recipient mice with the gut microbiota from healthy donors reversed pain hypersensitivity. Together, these data indicate that the gut microbiota from individuals with fibromyalgia is sufficient to cause pain in mice, suggesting the potential role of altered microbial communities in mediating distinct phenotypes in fibromyalgia patients.

P2-F-489: Characterization of the neural circuitry underlying context-dependent innate defensive behaviours

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Animals rely on fear responses to survive in natural habitats. In particular, prey species are required to respond to predatory threat through a series of innate defensive behaviours such as freezing and escaping. While recent studies highlight the neural mechanisms underlying instinctive escape behaviours, surprisingly little attention has been given to how environmental cues drive the control of these innate behaviours. Here, we demonstrate that the hippocampal projections to the anterior hypothalamic nucleus (AHN) mediate context-associated innate defensive behaviours. Furthermore, this work provides preliminary evidence which suggests unique roles for GABAergic and CaMKIIα+ AHN neurons in mediating context-associated escape behaviours. Using fiber photometry, we found that GABAergic and CaMKIIα+ AHN neurons show distinct dynamic response to predators, whereas only GABAergic neurons dynamically respond to contexts associated with predators. Moreover, optogenetic stimulation of CaMKIIα+ AHN neurons induced robust defensive behaviours. Lastly, anatomical tracing experiments revealed that both GABAergic and CaMKIIα+ AHN neurons project to the same topographic areas of the periaqueductal grey (PAG). Together, these results provide strong preliminary evidence that GABAergic and CaMKIIα+ AHN neurons utilize projections from the HPC and to the PAG to mediate context-associated memory and innate escape behaviours, respectively.

P2-F-490: The effect of pharmacological inhibition of the anterior paraventricular nucleus of the thalamus on cue-induced heroin seeking in male and female abstinent rats

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Relapse poses a substantial obstacle to addiction treatment, and the risk for relapse is exacerbated by chronic food restriction. However, the underlying neuronal mechanisms are not clear. Our laboratory examined the role of the paraventricular nucleus of the thalamus (PVT) in the augmentation of heroin seeking following forced abstinence in food restricted rats. There is ample evidence that the anterior (a) PVT and posterior (p) PVT subregions differ in their afferent and efferent pathways, and their function. We previously chemogenetically inhibited the aPVT and found no significant effect on cue-induced heroin seeking. Here, we aim to use pharmacological inhibition of the aPVT to validate our chemogenetic findings. Male (n = 15) and female (n = 17) Long Evans rats were trained to self-administer heroin for 10 days, followed by a forced abstinence period of 16 days. During forced abstinence, rats were either sated or food restricted (FDR). On day 15 of food restriction, rats were either injected with baclofen and muscimol into the aPVT or with vehicle (VEH), and underwent a heroin-seeking test under extinction conditions. Similar to our chemogenetic findings, pharmacological inhibition of the aPVT had no significant effect on heroin seeking in the FDR or sated groups. The lack of significant findings suggests that either the aPVT does not affect heroin-seeking behaviour under these conditions or that the aPVT serves as an inhibitory function. We plan to further explore the role of the aPVT using chemogenetic excitation.

P2-F-491: Development of novel dichoptic reading technology to treat amblyopia

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Current amblyopia treatment research is focused on binocular tasks instead of the usual patching treatment which has low compliance rates and is not effective across age groups. This study aimed to assess reading, a daily task, as a binocular treatment for amblyopia. Here, we developed a dichoptic e-book application as a framework to study the feasibility of this task for amblyopes. An application prototype was developed and uploaded onto tablets for participant assessments. Participants read e-books in anaglyph red/green/black presentation to allow for independent adjustments of monocular and binocular contrast. Amblyopic and control participants were then tested on their reading speed and questioned about their comfort using the application. We found that participants read slower in the dichoptic presentation than in the control presentation, indicating that their visual systems were forced to integrate information from both eyes. In some cases, reducing the contrast of text seen by the fellow eye also increased the reading speed of amblyopes in accordance with current research on binocular training approaches. Following the testing sessions that produced these results, participant feedback from the comfort questions was implemented into an improved application model. Overall, this study demonstrated that amblyopes can read binocularly within the e-book application framework suggesting that it could be an effective treatment for amblyopia. Future steps in this research are focused on training amblyopes on reading in this application to improve their binocular vision.

P2-F-492: Effect of emetine-mediated inhibition of protein synthesis on neural function in the hippocampus

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Memory consolidation has been studied for over one hundred years, yet the biological mechanisms remain enigmatic. A nearly axiomatic idea in the field of neuroscience is that, ultimately, the fixation of the synaptic changes thought to represent learning processes in the brain is completely dependent on the production of new proteins. This conjecture relies mainly upon behavioural studies of memory function using inhibitors of protein synthesis. However, growing evidence has shown that there are serious confounding influences of these types of drugs that might, in and of themselves, cause memory loss. Such effects include severe impairment of neurobiological function, including induction of apoptosis, disruption of synaptic release, and the inactivation of neural activity. Our lab has previously provided clarifying evidence on the inactivating effects related to the use of translational inhibitors. Intrahippocampal infusions of either anisomycin or cycloheximide at concentrations previously shown to induce amnesia were shown to produce profound and long-lasting silencing of synaptic and post-synaptic activity that was correlated with the extent of protein synthesis inhibition. In this study, we evaluated the impact of intrahippocampal administration of another translation inhibitor, emetine, on neural activity. Results indicated a marked reduction in hippocampal neural activity following a modest inhibition of protein synthesis, as measured by autoradiographic techniques. A correlation was observed between the extent of inhibition of protein synthesis and the magnitude of disruption in neural activity.

P2-G-494: Predicting which antigenic peptides may drive an autoimmune response in Parkinson?s Disease

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Parkinson's disease (PD) is a neurodegenerative disease with some immune components, including the presence of T cell clonal expansion and suggestions of T cell-neuron interactions. Although antigen-specific T cells against neuron peptides (such as α-synuclein) have been identified in PD, the repertoire of antigens which are involved in PD remains elusive. We conducted immunopeptidomic analysis of human iPSC DA neurons to reveal which proteins may serve as antigen sources during brain inflammation. This allowed for broad predictions of antigenic targets whereby identified proteins were analyzed for a variety of criteria to generate lists of predicted immunogenic peptides. I developed an algorithm based on four criteria: 1) ability of peptide to be favourably generated through cleavage, 2) ability to be presented by MHC, 3) ability to be recognized by PD-specific TCRs, and 4) similarity to PD-related pathogens. These criteria allowed for peptide ranking in terms of their likeliness to underlie a PD-specific, T cell-mediated immune response. Immunopeptidomes of 3163 neuron proteins were identified and using my novel prediction pipeline, we predicted the peptides most likely to be immunogenic in PD. Rankings also segregated peptides on a patient HLA level, allowing for peptide predictions based on the

HLA alleles of a given patient. This antigen discovery tool can be used for PD, as well as other diseases where autoimmune mechanisms are suspected.

P2-G-495: Evaluating glial cell response to functional microelectrode implants in vitro

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Insertion of functional microwire implants designed to interface with nervous tissue (e.g., intraspinal microstimulation) elicits an inflammatory response. Central to this response are glia, whose functions include surveillance and defense of the central nervous system. They are also responsible for gliosis, cell death, and glial scar formation that can exacerbate injury and prevent healthy recovery of tissue. The goal of this project is to develop a systematic approach to evaluating cell reactivity to implanted neural interface devices. We leveraged 2-dimensional cell cultures as a reductionist means of assessing glial cell reactivity to chemical and biological stimuli. We placed 75 µm diameter platinum/iridium electrodes with mouse mixed glial cell cultures in 12-well plates. This enabled the modelling of the glial scarring phenomenon, and served as an approach that has a reduced ethical footprint and complements in vivo testing. Time course experiments were performed to document cellular response to stimulation applied for 4 h/day over 1, 3, and 7 days. Live imaging experiments were also performed to track transgenic microglial morphology and movement in response to modified stimulation parameters. Microscopy and cytokine secretion profiles assessing mixed glial response to embedded electrodes suggest localized responses at the electrode-culture interface, and support published in vivo results. Using such a platform for testing biocompatibility of different design iterations of wires and stimulation patterns will allow for improvements in implant safety and longevity.

P2-G-497: A SOX10-mOrange reporter iPSC line to study and enhance in vitro differentiation of oligodendrocytes and progenitor cells

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Oligodendrocytes (OLs) are the myelinating cells of the central nervous system. Their main function is to insulate axons of neurons. OLs and their progenitors (OPCs) are commonly implicated in neurological disease, suggesting these cells are uniquely vulnerable. While OLs have been well studied in murine models, these findings do not always translate to humans. Use of human-derived induced pluripotent stem cells (iPSCs) allows for the study of human OLs. Growth factor-based iPSC-OL differentiation protocols are characterized by high variability, contaminating astrocytes, and low yield of mature OLs (MBP+), rendering their use as an in vitro model difficult. We developed a gene-edited iPSC reporter line (SOX10-mO), in which endogenous mOrange fluorescence is detectable upon translation of SOX10. We can employ live cell sorting to purify and categorize our culture according to lineage maturity level. Using a widely accepted protocol, we tested the differentiation efficiency of SOX10-mO cells. Characterization

of the progenitor stage revealed GPCs, bipotent precursors of astrocytes and OPCs. Differentiation of GPCs revealed a subpopulation of late O4+ OPCs, corresponding to an increase in SOX10 expression. Most cells failed to reach maturity, suggesting this protocol can produce reliable OPCs but not MBP+ OLs. We present a protocol using the SOX10-mO system to trial changes with the goal of improving efficiency and reproducibility, including subtraction of thyroid hormone T3 from the progenitor media until maturation phase and testing of a novel maturation medium capable of producing differentiated OLs. We present a robust protocol capable of producing terminally differentiated OLs that lays the foundation for future disease modeling of these cell types.

P2-G-498: High-level executive control signals in the human posterior thalamus? a causal investigation using non-invasive transcranial ultrasound stimulation

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The thalamus was traditionally thought of as a passive relay for transmitting information to the cortex. Recent animal studies have challenged this view by showing that manipulations of the thalamus affect executive functions. In the past, it was not feasible to causally study potential roles of the human thalamus in executive functions as traditional non-invasive brain stimulation (NIBS) methods could not target this structure. Using transcranial ultrasound stimulation (TUS), which has now made it possible to target deep brain areas, here we test the hypothesis that the human pulvinar, a posterior thalamic nucleus, plays an active role in executive functions such as attention and response inhibition. Participants performed visual search and stop-signal tasks before and after TUS on both pulvinars. We used BabelBrain (a Python-based application) to plan an optimal trajectory for sonication, compensate for ultrasound attenuation due to the skull, and ensure the acoustic intensities and thermal rise in individual subjects are within the safety range. A theta burst TUS protocol successfully impacted executive functions in both tasks. Theta burst TUS hampered efficiency in the visual search task and prolonged stop-signal reaction times in the stop-signal task. These preliminary results support the notion that the human thalamus plays an active role in executive functions, most likely by regulating cortical activities, and also demonstrate that TUS has great potentials to causally investigate functions of deep brain areas that cannot be targeted by other NIBS techniques.

P2-G-499: Novel intracerebroventricular infusion method for corticosterone administration in neonatal mice

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Early life stress (ELS) has profound effects on brain development and function. Glucocorticoids (GCs) are steroid hormones secreted by the adrenal glands during stress. The negative effects of ELS are thought to

be mediated by adrenal GCs such as corticosterone, the predominant GC in mice. However, there is a period of adrenal quiescence in early life (approximately postnatal day 2-12 in mice), when extra-adrenal organs such as the brain, locally produce GCs. Some forms of ELS elevate GCs more in the brain than in the blood. Most ELS paradigms administer GCs systemically, no study has administered GCs directly to the neonatal brain in vivo. Here, we developed a novel technique to administer corticosterone directly to the neonatal brain via a single unilateral intracerebroventricular (icv) infusion. Local anesthetic was applied to the scalp of male and female postnatal day 5 C57BL/6J mice for 8 min. Then, 2µL of either saline (vehicle control), 100ng or 150ng of corticosterone was administered (n=8/group) via an icv infusion. The brain and blood were collected after 2.5 hr. Corticosterone levels were assessed in microdissected brain regions and blood via liquid chromatography tandem mass spectrometry (LC-MS/MS). Preliminary results suggest that higher doses of corticosterone increase brain corticosterone levels, while blood corticosterone levels remain low. Our study provides a novel technique to administer corticosterone, and other neuromodulators, directly to the neonatal mouse brain without general anesthesia, which is a potent stressor that increases circulating GCs.

P2-G-500: Development of a single-cell RNA sequencing strategy for transcriptomic analysis of brain vasculature cells in an Alzheimer's disease mouse model

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Alzheimer's disease (AD) is the principal cause of age-related dementia. Its impact on the brain's vasculature has been described but deeper investigation is needed to understand the involvement of these changes in disease progression and to what extent they can be reversed by potential therapeutic avenues, such as exercise (EX). Single-cell RNA-sequencing (scRNA-seq) is a powerful tool for evaluating how the transcriptomes of individual cell types within a complex tissue are altered by disease and/or treatments. Here, we developed a scRNA-seq strategy to investigate the effects of AD and EX on vasculature-associated cells. Using the microwell-based BD Rhapsody single-cell platform, we established and validated a novel approach for examining the transcriptome of vasculature-associated cell types (endothelial cells, pericytes, astrocytes and microglia). Subclustering permitted the successful identification of cells associated with distinct subtypes of vasculature (arteries, veins and capillaries). Using this strategy, we are currently characterizing vasculature-associated transcriptomic changes in the 5xFAD model of AD and the potential acute and chronic effects of EX on these cell types. These studies will provide new insights into avenues of protecting the vasculature and brain during AD.

P2-G-501: Development of a haptic glove to investigate auditory-tactile integration and multimodal plasticity

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Objective: This presentation showcases the ongoing development and validation of a vibrotactile glove. The specific objectives are to explain the broader objectives of the project and present an overview of the design process, challenges encountered, and initial testing results. Background: Hearing and touch are closely related. Vibrations can propagate through the air and be heard as sound via the auditory system but can also be felt as touch directly through cutaneous mechanoreceptors. The purpose of the haptic glove is to investigate the integration of auditory and tactile sensations in the brain, with a particular focus on understanding the effect of multimodal plasticity that can occur through training (e.g., in musicians) or through sensory deprivation (e.g., hearing loss). Methods: Tactile threshold measurements were conducted for sinusoidal vibrations between 100 and 1000 Hz applied to the dorsal skin of the fingers and to the palm of the hands using the vibrotactile glove. Results: Preliminary results show frequency response curves that are coherent with the existing literature. Threshold appear to vary between subjects and actuator localization, but not between hand. The variability can be attributed to both physiological factors and to limitations of the current prototype. Conclusions: The limitations of the current haptic glove prototype can guide its ongoing development. The results from the threshold assessment help to design of new experiments, such as imaging studies and behavioral experiments involving musicians and people with hearing loss.

P2-G-502: Using natural sounds to assess hyperacusis and misophonia

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The main objective of the presentation is to present the development of a new method to assess hyperacusis and misophonia using natural sounds. Currently, hearing healthcare professionals, such as audiologists, rely on semi-structured interviews, standardized questionnaires, and their clinical judgments to assess the presence of hyperacusis and misophonia. There is no objective diagnostic measure or biomarker for these disorders. The test consists in presenting pleasant and unpleasant natural sounds at four intensities (60-, 70-, 80- and 90-dB SPL) through headphones and asking the patient to rate the pleasantness of the sound on a visual analog scale from 0 (Very pleasant) to 100 (Very unpleasant). If a sound is rated very unpleasant (>90) at a certain level (e.g., 60 dB SPL) it is not presented at higher levels (e.g., 70, 80, 90 dB SPL.). "Misophonic" trigger sounds such as chewing, sniffling and slurping were included to the list of the sounds presented. In two published studies (Enzler, Fournier, et al., 2021; Enzler, Loriot, et al., 2021), the pleasantness ratings of hyperacusis and misophonia patients were compared to matched controls to identify the most discriminant sounds, that is, the sounds that provided the best sensitivity (SEN) and specificity (SPE) for each disorder. Seven sounds were identified for hyperacusis (SEN: 81%, SPE: 88%) and ten sounds for misophonia (SEN: 95%, SPE: 87%). The diagnostic tests developed here directly measures the lived experience following the presentation of a natural sound and determine which sounds are unpleasant for a given patient and how loud they are perceived. This validates patients' complaints and may help with personalized interventions.

P2-G-503: Exploring the intricacy of neurodegenerative disorders: The advantages of long-read sequencing

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Despite a rapid evolution of technologies available in clinical settings, such as next-generation sequencing, only 20-50% of patients with rare neurological disorders obtain molecular diagnoses following standard testing. One of the major obstacles is the complexity of interpreting variants of unknown significance (VUS). We propose that long-read sequencing (LRS) can efficiently bridge the identification of VUS and the assessment of their impact through its multiple applications. A cohort of eight undiagnosed patients with complex episodic ataxias were recruited following a thorough yet unsuccessful clinical investigation. DNA, RNA and proteins were extracted from peripheral blood mononuclear cells, enabling the combination of whole-genome and RNA-sequencing, as well as validation experiments such as LRS. The multi-omics approach identified excellent candidates in each patient, four of which have been functionally validated (4/8; 50%). An interesting result is the diverging contexts in which LRS was used to evaluate the effect of VUS: demonstrating a trans configuration of two SPG7 variants, proving the alternative splicing and transcriptome shift of ELOVL4 and PMPCB in two patients, and precisely quantifying ATXN2 repeat expansion in another case. This adaptability was a major factor in its capacity to contribute to the functional validation. These results highlight the potential of multi-omics and LRS in the context of clinical genetics. Additionally, they have a direct impact on patients through the psychological relief linked to an official molecular diagnosis, a better understanding of the pathology, and better care management. Finally, these findings may hopefully lead to novel therapeutic targets in the future.

P2-G-504: Comparing M1 and V1 microcircuit connectivity with two-photon optomapping

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Neuronal connectivity patterns determine information processing in the brain, and yet are poorly studied. Unfortunately, the current state of the art for measuring microcircuits -- multiple patch clamp -- is inefficient for large-scale microcircuit mapping. We, therefore, created a high-throughput two-photon optogenetic mapping technique: optomapping. We previously optomapped primary visual cortex (V1) -- a key neocortical input area. Here, as a comparison, we optomap primary motor cortex (M1) -- a key neocortical output area. To activate M1 pyramidal cells (PCs), we injected AAV9-EF1a-DIO-STChroME-P2A-mRuby into M1 of postnatal day(P)1-2 Emx1Cre mice. In acute M1 slices from P18-P25 injected mice, we used two-photon spiral scans at 1040 nm to activate candidate presynaptic PCs, while looking for postsynaptic responses in patch-clamped PCs. Inputs from layer (L) 2/3 and L5 PCs onto L5 PCs did not differ in synaptic response (29/669=4% onto 5 PCs; L2/3 mean=0.19±0.1mV; L5 mean=1.1±0.3 mV, p=0.24), paired-pulse ratio (35 inputs onto 5 PCs; L2/3 mean=1.0±0.2; L5 mean=0.83±0.1, p=0.48), and layer connectivity (L2/3 mean connectivity=2.3±1%; L5 mean connectivity=4.3±0.7%, p=0.28). Comparing L5 PCs in V1 and M1, we found indistinguishable distributions of synaptic responses (Kolmogorov-Smirnov, p=0.17) and radial connectivity (p=0.52). Taken together, our findings highlight how M1 and V1 microcircuits in fact share many properties, despite the striking functional differences of these areas.

P2-G-505: Title: High channel count electrode arrays for recording large populations of primate motor units during naturalistic movements

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A central goal of neuroscience is to discover how the central nervous system controls muscles to produce behavior. While the muscle is a common end-effector in the animal kingdom, it is utilized in amazingly flexible ways, varying tremendously across species and across effectors within species. However, our understanding of the neural mechanism underlying the control of muscle is still limited because we lack an established technology to simultaneously record large populations of individual motor units (MUs) during natural behavior. To elucidate neural control of species-specific commonalities and specialization of muscle functions, we developed a novel injectable electrode array for simultaneously recording individual MUs in humans and non-human primates on a large scale with fine temporal resolution, building on previous designs optimized for chronic recordings in rodents and songbirds. The injectable array consists of 32-channels, with a pair of contacts (740 um apart) linearly distributed in 16 rows over 167 mm length. We could acutely record MU activity by inserting the array into the muscle with a 25-gauge cannula. This approach is functional both in non-human primates and human subjects, and we successfully recorded as many as 20 MUs from proximal and distal arm muscles during naturalistic movements such as reaching, counteracting mechanical perturbations, and finger movements. We further discuss current issues associated with the data collection and analysis pipeline including customized electrodes for different muscles and spike sorting methodologies for MU data.

P2-G-506: Single-nucleus transcriptomic and epigenetic analysis of rat hippocampal cells following amyloid-beta oligomer injections

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Alzheimer's disease (AD) is a neurodegenerative disease characterized primarily by the aggregation of amyloid-beta (Aβ) oligomers and neurofibrillary tangles. Accumulation of Aβ oligomers is detected 10 to 15 years before the appearance of the first clinical symptoms of AD. Studies have shown that Aβ oligomers are involved in synaptic and neuronal losses observed in the hippocampus, a brain region critically involved in memory that is affected in the early stages of AD. Here, we investigated the impact of Aβ oligomers on the different cell types present in the hippocampus using a rat model. Aβ oligomers were injected daily into the hippocampus for 0, 2, 4 or 6 days. Subsequently, the brains were dissected and cut using a cryostat. Cells located directly under the injection site were then collected by laser microdissection. The nucleus were isolated and we performed a transcriptomic and epigenetic analysis simultaneously on each of these nucleus (single nucleus RNA-seq ATAC-seq; 10xGenomics) coming from neurons, astrocytes, oligodendrocytes, pericytes, endothelial cells and microglia. This study will allow to determine the gene expression and epigenetic changes induced specifically by Aβ oligomers in each

hippocampal cell type during the progression of Aβ pathology. This could pave the way to find new therapeutic targets efficient in the early stages of AD.

P2-G-507: 2-photon optogenetic mapping of visual cortex microcircuits

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Connectivity and synaptic dynamics are fundamental to information processing in the brain. Multiple patch clamp has long been the state-of-the-art technique to study local connectivity, but only yields a few connections per day. Elucidating entire microcircuits in different states (e.g., pathologies) has thus been prohibitively difficult. As a solution, we combined 2-photon optogenetics with patch clamp to develop optomapping, a high-throughput connectivity mapping method. We injected AAV9-CAG-DIO-STChroME-P2A-mRuby in P1 Emx1-Cre mice to express the soma-targeted opsin ChroME in pyramidal cells (PCs) in primary visual cortex (V1). In P18-P25 acute slices, we used 1040-nm Ti:Sa spiral scans to drive PCs with single-cell and millisecond resolution. Evoked EPSPs were recorded in PCs, basket cells (BCs), and Martinotti cells (MCs). In each cell, we mapped dozens of inputs across all cortical layers, revealing cell-type-specific connectivity rates and synaptic dynamics. Postsynaptic cells were classified by spike pattern and morphology. With optomapping, we found that L5 BCs received stronger local excitation (90/240=37.5%; 2.2±0.4 mV; n=275 inputs onto 7 cells) than L5 PCs (120/569=21.1%; 0.67±0.1 mV; n=188 inputs, 12 cells) and MCs (28/167=16.8%; 0.37±0.1 mV; n=56 inputs, 5 cells). We also found that short-term plasticity of PC inputs onto MCs and BCs depended on layer of origin. We verified the canonical PC-PC circuit, but the PC-BC and PC-MC circuits deviated from this. We conclude that optomapping enables rapid large-scale mapping of local circuits in different conditions.

P2-H-508: Assessment of the Quality and Reach of AMiNDR Podcast, An Open-Access Knowledge Dissemination Tool for Neuroscientists

Anusha Kamesh[1], Joseph Liang[2], Sarah Louadi[2], Ellen Koch[2], Elyn Rowe[2], Naila Kuhlmann[1], Lara Onbasi[3], Judy Cheng[2], Jacques Ferreira[4]
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Podcasting has grown in popularity as a means to communicate science within and beyond the research community. They serve as tools to remain informed, entertained, and connected; and can complement written and other audiovisual material. Our podcast, AMiNDR (A Month in Neurodegenerative Disease Research), harnesses the potential to reach across disciplines and geography to communicate the latest science behind Alzheimer's disease (AD) research in an accessible way. Having spent three years developing AMiNDR to reach AD researchers and clinicians, we ask: What makes podcasts an effective knowledge dissemination tool? We tracked the growth of our listenership using podcast analytics on Simplecast in response to various strategies to improve our reach and content quality. These strategies include external engagement and internal review. Here, we discuss formal feedback from listeners

gathered by voluntary surveys between 2021 and 2023 to assess the efficacy of AMiNDR as a knowledge dissemination tool. We also report on the effects of implementing an internal review process measured through feedback gathered from one-on-one interviews with team members. The implementation of these strategies are correlated with the growth of our podcast, as we now have an average of over 80 listeners per episode, up from 50 listeners in 2021. In continuously improving the quality of our podcast, as well as working to extend our global reach, we share our refined understanding of how a podcast can serve as a useful and accessible means of knowledge dissemination as it pertains to AD research.

P2-H-509: ?Think Twice?: A graduate student-run podcast uncovering the truth behind mainstream media coverage of neuroscience

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Accessible and trustworthy science communication resources are crucial for improving public understanding of neuroscience. While social media has the capability to rapidly circulate obscure and misleading information and disinformation, it also offers the unique opportunity for impactful public engagement and awareness. A new outreach program from graduate students at the Centre for Neuroscience Studies at Queen's University has developed the podcast, 'Think Twice,' with the goal of bringing more nuance and rigor to neuroscience coverage in mainstream media. Our objective is to address a variety of topics related to cutting edge research or controversies in the field of neuroscience. We have prepared a season of 4-6 episodes to be published in spring 2023 and are preparing an exciting public engagement campaign across social media platforms. Topics include psychedelic-assisted psychotherapies, dishonesty in scientific publications, the future of brain-computer interfaces, and the emerging fields of neurolaw and neuroethics. Overall, 'Think Twice' aims to have a positive societal impact by breaking down barriers to the dissemination of scientific information, giving early-career neuroscientists a voice, and fostering a culture of accessible science communication and entertainment.

P2-H-510: An RDoC approach to dangerousness in forensic psychiatry populations: understanding empathy via epigenetics

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INTRO: In Canada, individuals recognised by Court to be NCRMD (not criminally responsible on account of mental disorder) can enter forensic psychiatry hospital for rehabilitation. The ability to predict future dangerousness is paramount to their eventual community reinsertion. </br> SUMMARY:To achieve a better understanding of the factors predictive of dangerousness in NCRMD patients, we propose adopting the NIMH Research Domain Criterion (RDoC) framework (integrating various levels of information: genetic, molecular, behavioural, psychological, and clinical). As a steppingstone, we illustrate this through a review of existing literature on the epigenetic mechanisms known to affect the

oxytocin receptor gene (OXTR) associated with empathy. We suggest that psychosocially triggered epigenetic alterations to the OXTR gene response could have direct clinical implications in forensic psychiatry patients' risk of violent behaviour, regardless of their DSM-V psychiatric diagnoses. Indeed, NCRMD patients' level of dangerousness may at least in part be predicted by epigenetic changes to the OXTR gene, in turn resulting from their developmental history and past psychosocial environment, as well as genetic and neuroanatomical specificities. These characteristics may affect their capacity for empathy at different levels of analysis. </br> CONCLUSION: This RdoC approach to dangerousness has the potential, in the future decades, to allow the integration of precision medicine into both forensic psychiatry research on prediction of future dangerousness and eventually clinical forensic psychiatric work with NCRMD patients.

POSTER SESSION 3

P3-A-511: Sex-and Age-related distribution of Sigma-1R expression in the mouse brain

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Sigma-1R (S1R) is a ubiquitous chaperone protein expressed in various brain regions, such as the hippocampus, amygdala, and striatum. Via its ligand-dependent (e.g., neurosteroids, especially sex steroids) and -independent activities, S1R engages in various signaling pathways that regulate several cellular and brain functions (e.g., protein homeostasis, neuronal excitability, synaptic plasticity, memory processes, and mood regulation). It is well-established that cellular mechanisms modulating S1R functions during aging are not static but continuously subjected to the ever-changing physiological milieu, which affects the expression and activity of critical proteins and hormones. Interestingly, S1R has been shown to affect these processes in a sex-specific manner during aging. S1R is also related to, and even identified as a causative agent of several chronic neurological disorders such as neurodegenerative diseases, memory impairment, and depression. Despite its critical functions, S1R expression profile in the brain throughout lifespan has yet to be explored. To fill this gap, we performed immunofluorescence labeling and confocal imaging to provide a map of S1R expression in the brain at different ontogenetic stages (juveniles, young and middle-aged adults) using both male and female mice. Our preliminary data show that S1R is densely expressed in the hippocampus and striatum of male and female juvenile mice, and dramatically decreases during adulthood. These results correlate with the locomotor and cognitive function impairments observed in mice lacking S1R.

P3-A-512: Cell division orientation regulates tissue size in the developing retina and neocortex

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The accurate regulation of cell number and identity during development is critical for the formation of a fully functional nervous system, but the mechanisms coordinating it remain ill defined. In the developing

neocortex, the regulation of cell number involves different subtypes of progenitors undergoing mitosis at various apico-basal locations, whereas retinogenesis is achieved by a single type of equipotent apically dividing progenitor. Interestingly, the cortical expansion observed in humans is thought to be achieved by basal progenitors called outer Radial Glial Cells (oRGC), which are produced by radial glia dividing with their mitotic spindle aligned 'vertically' along the apico-basal axis. Whether vertical divisions are sufficient to generate basal progenitors in other CNS regions like the retina remains unknown. Recently, we showed that the G-protein signaling modulator GPSM2 and the adaptor protein SAPCD2 regulate cell division orientation. To explore their involvement in basal progenitor production, we generated Gpsm2/Sapcd2 double knock-out mice (dKO) and studied retinal and cortical development. We found a drastic switch from horizontal to vertical divisions which was accompanied by an overproduction of basal progenitors and hyperplasia in both tissues, including the generation of an extra neuronal layer. Using single-cell RNA sequencing, we found that progenitors generated in the dKO cortex present oRGC features while the identity of retinal basal progenitor remains more elusive. However, it seems that in both cases the Hippo pathway is affected. These findings show that vertical divisions are sufficient to the production of basal progenitors in the retina and neocortex, and identify a common mechanism regulating tissue size through division orientation.

P3-A-513: MicroRNAs and the integration of guidance cues during regeneration

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During development and regeneration, neurons must establish connections with their appropriate target cells. This process begins with neurite extension, directed by growth cones, which are structures located at the leading edge of growing neurites. Growth cones contain the machinery necessary to sense, interpret and integrate various guidance cues, allowing them to rapidly re-direct axon outgrowth. The vitamin A metabolite, retinoic acid, is essential for proper brain development and is known to promote neurite outgrowth in mammalian neurons. We have previously shown that retinoic acid is involved in growth cone guidance during regeneration of invertebrate neurons. Retinoid-induced growth cone turning is dependent on local protein synthesis and involves a small non-coding microRNA (miR-124). This study now investigates how growth cones respond to retinoids in the presence of other known guidance cues. We present evidence of altered growth cone sensitivity to retinoic acid following exposure to a negative guidance cue and are now determining the role of miR-124 in this altered response. Using in situ hybridization, the spatial and temporal expression patterns of miR-124 at various stages of retinoid-induced growth cone guidance are examined. These experiments will help us further understand the molecular mechanisms regulating growth cone guidance by retinoids, and how this unconventional guidance cue might interact with other cues present in the nervous system.

P3-A-514: Perinatal estrogen differentially masculinizes expression of astroglial markers in the developing neocortex

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Astroglial cells are important mediators of various aspects of neurodevelopment including building, maintaining, and modulating neuronal circuits underlying complex behaviours in the neocortex. Astroglial cells express specific proteins and genes that pertain to their morphology, function, and maturation. In addition, astroglia express receptors that respond to gonadal hormones responsible for masculinization of the brain and behaviour, namely estrogen. We have previously shown there are sex differences in active gene translation in astroglial cells at postnatal day 7 in mice, a period of astroglial maturation. Here we examine if perinatal estradiol administration in female mice is sufficient to masculinize astroglial protein and/or gene expression observed at P7. We observe that canonical astroglial markers like glial fibrillary acidic protein and glutamine synthetase do not show sex differences and are not affected by perinatal estrogen, but markers of astroglial maturation, Aldh1a1, and astroglial stem-like potential, i.e. the s-phase marker of cell division, Ki67, and the cytoskeletal protein associated with nuclear remodelling, vimentin, show sex differences and can be masculinized by perinatal estradiol administration. These results indicate that some sex differences in neocortical astroglia are at least in-part due to the role of masculinizing estrogens. Given neurodevelopmental disorders are highly prevalent in males compared to females in human populations and that astroglia are involved in virtually all neurodevelopmental disorders, these results highlight the importance of masculinization of the brain as a potential mediator of neurodevelopmental disorders. Further research is needed to determine other contributions to sex differences in astroglia.

P3-A-515: Following topographic map formation in the developing Xenopus retinotectal system

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The retinotectal projection in the Xenopus visual tectum is topographically organized. Neurons in the retinotectal system undergo extensive activity-dependent plasticity during early development, which is believed to refine the retinotopic map to form a more precise representation of the visual world. We have previously observed marked changes in the three-dimensional layout of the retinotopic map within the tectal volume over a span of several days in development. To examine this change in the context of single tectal neurons, we performed calcium imaging in the optic tectum of GCaMP6-expressing Xenopus laevis tadpoles where tectal cells were sparsely labelled with Alexa Fluor 594 dextran dye. Animals were imaged at stage 45 and again at stage 48, a period during which extensive tectal growth and robust activity-dependent plasticity occurs. We recorded the morphology of the dextran-labelled cell and performed visual receptive field mapping to extract the functional retinotopic map in the same tectal volume. By observing the position of the dextran-labelled cell in relation to the topographic map, as well as the response of the labelled cell to positioned visual stimuli, we expect to gain insight on whether changes in retinotopic map layout are a result of cell addition and migration, or shift in receptive field representations at the level of individual cells.

P3-A-516: Early Life Stress Modifies the Function of the Medial Prefrontal Cortex during Fear Conditioning in Juvenile Rats

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Exposure to early life stress (ELS) can exert long-lasting impacts on emotional regulation. The medial prefrontal cortex (mPFC) plays a key role in fear learning and is highly sensitive to environmental stressors throughout development. Using the limited bedding paradigm (LB) between postnatal days (PND)1-10 as a model of ELS, we examined the functional consequences of ELS on excitatory and inhibitory tone in the prelimbic (PL) mPFC. We measured glutamate concentrations during fear conditioning using in vivo microdialysis in freely behaving juvenile (PND28-32) rats. We report that LB exposure tends to diminish fear-induced glutamate response in the PL mPFC of juvenile males, but not females. To estimate ELS effects on the fear-induced activity of parvalbumin (PV) and somatostatin (SST) interneurons, we determined the density of cFos/PV co-expression and cFos/SST co-expression after fear conditioning using immunohistochemistry. We found that cFos activation in SST, but not PV interneurons in the PL mPFC was elevated after fear conditioning only in juvenile males that were exposed to LB condition, but not in control animals. These results suggest that ELS might alter excitatory/inhibitory balance in the PL mPFC during fear conditioning in juvenile male, but not female rats. Supported by CIHR PJT162376 to CDW.

P3-A-517: Altered interneuron migration dynamics in a novel mouse model of PIGB associated epileptic encephalopathy

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Pathogenic mutations in PIGB were recently described in children with epileptic encephalopathy and inherited GPI anchor biosynthesis defect. GPI anchors have been reported to be critical for proper neuronal migration during neurodevelopment. Although GPI anchor deficiencies have been associated with epilepsy, little is known about the underlying cellular and molecular mechanisms. We generated a conditional knock-out mouse model (Nkx2.1Cre;Pigbc/c;RCEEGFP) which recapitulates the epileptic and behavioral phenotypes seen in patients. Specifically, spontaneous seizures were observed in mutant mice, as well as anxiety-like hyperactivity and altered spatial learning. We also found a significant reduction in the number of cortical interneurons in the postnatal somatosensory cortex at different ages (P0, P7, P21), which suggested a potential migration deficit. Using high-resolution time-lapse live imaging of medial ganglionic eminence (MGE) explant cultures, we show that a prenatal deletion in PIGB alters interneuron migration dynamics and complexifies their morphology. Organotypic brain slice cultures are being conducted to further characterize this cellular phenotype in a three-dimensional model. Experiments to dissect potential effectors are underway. This study will clarify the pathophysiology of PIGB associated epileptic encephalopathy as well as deepen our understanding of the role of GPI-anchor-related pathways in neurodevelopment and more specifically, in the migration of cortical GABAergic interneurons.

P3-A-518: Hmgb1 regulates astrocyte morphogenesis and cerebrovascular maturation

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Astrocytes are closely linked with the brain vasculature, a critical relationship for neuronal health and function. However, key astroglial factors driving these physical and functional associations during development have not yet been identified. Here, we leveraged pan-astrocytic gene Aldh1L1 as a molecular handle to unmask gliovascular dynamics in the postnatal mouse brain. We found by immunofluorescence and electron microscopy that, past postnatal day 5 (P5), astrocytes undergo extensive maturation and then interact with vessels more closely from P7 with their endfeet. Astrocytic endfeet undergo refinement between P7 and P14, after which endfeet exhibit a mature morphology. To identify astrocyte genes critical for gliovascular development during postnatal brain growth, we utilised TRAPseq and multiplex spatial RNA sequencing in the cerebral cortex of P0, P5 and P14 mice. We consistently found that High-mobility group box 1 (Hmgb1), normally involved in vascular repair post-injury in the adult brain, was highly expressed in astrocytes at birth and decreased rapidly. Astrocyte-selective ablation of Hmgb1 in newborn mice led to transcriptional changes in astrocytes related to cytoskeletal remodeling, affected astrocyte morphogenesis and endfoot placement, and altered endfoot protein distribution. While lack of astroglial Hmgb1 did not affect microvascular permeability or angiogenesis postnatally, it impaired neurovascular coupling and behaviour in adults. These findings reveal a novel mechanism regulating gliovascular maturation during postnatal brain development.

P3-A-519: Single-cell approaches to understand the evolution of oligodendrocyte precursor cells during development and following adult demyelination

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Developmental myelination occurs postnatally via genesis of oligodendrocyte precursor cells (OPCs) that make oligodendrocytes (OLs). Myelination also occurs in the adult brain following demyelinating injury, in part via adult OPCs that are generated neonatally. However, little is known about how this adult OPC pool is established. Using single-cell RNA sequencing (scRNA-seq) and single-cell ATAC sequencing (scATAC-seq), we demonstrate that the early postnatal murine cortex contains two transcriptionally and epigenetically distinct populations of OPCs. One population appears metabolically active and primed to differentiate (activated or actOPCs), whereas the second is more metabolically quiet and is primed for expression of genes involved in synaptic function (long-lasting or lOPCs). By contrast, the adult cortex contains a single OPC population that is highly similar to neonatal lOPCs, but with chromatin in a more closed state. Notably, following cuprizone-induced demyelination, the adult OPCs do not reacquire a development-like open chromatin state, but instead maintain their adult uninjured state. These findings,

combined with trajectory inference, support a model where developing neural precursors give rise to actOPCs, which then either differentiate into OLs or form lOPCs. These neonatal lOPCs then close down their open chromatin state to establish adult OPCs, forming a pool for the generation of OLs following injury. Thus, our data identify a developmental lineage for adult OPCs, and suggest that OPC-mediated myelination differs during postnatal versus adult life.

P3-A-520: rAAV-CRISPRa therapy corrects Rai1 haploinsufficiency and rescues selective disease features in Smith-Magenis syndrome mice

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Haploinsufficiency in retinoic acid induced 1 (RAI1) causes Smith-Magenis syndrome (SMS), a syndromic autism spectrum disorder characterized by neurocognitive deficits and obesity. Currently, curative treatments for SMS do not exist. Here we take a recombinant adeno-associated virus (rAAV)-clustered regularly interspaced short palindromic repeats activation (CRISPRa) approach to increase expression of the remaining intact Rai1 allele. Building upon previous work that found the paraventricular nucleus of hypothalamus (PVH) plays a central role in SMS pathogenesis, we performed PVH-specific rAAV-CRISPRa therapy by increasing endogenous Rai1 expression in SMS (Rai1 /-) mice. We found that rAAV-CRISPRa therapy rescues excessive repetitive behavior, delays the onset of obesity, and partially reduces hyperphagia in SMS mice. Our work provides evidence that rAAV-CRISPRa therapy during early adolescence can boost the expression of healthy Rai1 allele and modify disease progression in a mouse model of Smith-Magenis syndrome.

P3-A-521: Investigating the role of the prelimbic cortex in developmental fear conditioning

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The prefrontal cortex (PFC) undergoes dynamic and extensive anatomical and synaptic changes across early life. The prelimbic cortex (PL) subdivision of the PFC and its projections to the basolateral amygdala (BLA) are particularly important for the expression and retrieval of fear memories in adult rodents. However, fear learning is developmentally regulated, and some evidence points to younger animals not requiring the PFC for fear regulation. Since existing research on the role of the immature PFC in fear processing is very limited, we investigated when the PL and PL-BLA pathway are recruited for fear conditioning. We chemogenetically inhibited the PL and PL-BLA pathway in infancy (postnatal day (P) 15) and adolescence (P30) during fear training and tested for fear retrieval and contextual fear the following day. We found that while infant mice were unaffected by this manipulation, adolescent mice showed impaired fear retrieval when inhibiting the PL and PL-BLA pathway during fear conditioning. Furthermore, fear training led to an increase of AMPA:NMDA ratios in PL-driven responses in BLA principal neurons only in P30 animals, consistent with an absence of PL-BLA recruitment for fear learning by P15. Taken together, our results suggest that the PL-BLA pathway is only recruited to support fear encoding between infancy and adolescence. Understanding the contribution of the PFC to fear

processing in early life will provide insight into normative circuit maturation and emotional learning across the lifespan.

P3-A-522: Manipulating seizure-sensitive neurons to rescue early seizure-induced target-specific modification of hippocampal CA2 excitatory circuits

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Early life epilepsy is often refractory to current treatments leading to later life epilepsy and long-term cognitive impairments, including social recognition deficits. Sitting between the CA1 and CA3, the hippocampal CA2 is essential for social recognition memory processing. However, how CA2 neurons are affected in early life seizures remains completely unknown. Using an established PTZ seizure model, we demonstrated for the first time an age-dependent seizure vulnerability of CA2 cells. Seizures in adult mice did not induce significant alteration of AMPAR function in CA2 neurons, while seizures in immature mice significantly enhanced AMPAR function of CA2 neurons by regulating perforant pathway-specific presynaptic glutamate release, and impaired pre-weaning social recognition memory. An AMPAR antagonist, NBQX, rescued early seizure-induced AMPAR function enhancement and associated social recognition deficits. Importantly, using a c-Fos-GFP based transgenic mouse model, we showed direct evidence for selective activation of a subpopulation of CA2 neurons in early seizures. We confirmed early seizure-induced AMPAR enhancement occurred selectively in activated GFP+ neurons compared to non-activated, GFP-ve, and control cells via strengthening perforant pathway-specific glutamatergic circuits. Importantly, precise chemogenetic suppression of seizure-sensitive neurons reversed early seizure-induced AMPAR enhancement and pre-weaning social recognition deficits. Our results strongly support a critical role of seizure sensitive neurons in early life seizure-induced neuronal circuit reorganization and social recognition deficits.

P3-A-523: Developmental axonal swellings depend on action potential propagation signalling

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The development of axons and the establishment of contacts between neurons is an important step during brain development and the subsequent formation of functional brain circuits. Recently we demonstrated that axonal swellings appear transiently on cerebellar Purkinje cell axons during postnatal development where they propagate action potentials with higher fidelity and are associated with enhanced cerebellar function. An understanding of how axonal swellings form is thus important. We aimed to further investigate the role of firing in the formation of axonal swellings. We performed 2-photon time-lapse imaging in acute cerebellar slices from juvenile mice (P10 - P14) and added sub-saturating levels of tetrodotoxin (TTX; 1, 2.5, 5 and 10 nM) to parametrically block different concentrations of Na+ channels and as a result, impair action potential propagation in the axon to different degrees. Paradoxically, we found that low concentrations of TTX that block fewer somatic action potentials resulted in more axonal swellings that formed faster. Higher sub-saturating concentrations of

TTX blocked more somatic action potentials but resulted in fewer and slower-forming axonal swellings. Our results support a model in which action potential propagation failure is required for axonal swelling formation, but a balance between successful action potentials and failures exists. These data suggest that mild impairment of action potential propagation may be the optimal trigger to activate signalling cascades to form swellings and boost action potential fidelity.

P3-A-524: High-throughput clonal tracing reveals early post-natal neocortical cell fate transitions at single-cell resolution

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While neocortical embryonic neurogenesis has been well studied, early postnatal cell fate transitions, including gliogenesis, remain under studied. During the late embryonic/early postnatal (LE/EP) time period, ventricular zone (VZ) radial glia (RG) cells end production of cortical layer excitatory neurons, and switch to producing glia which populate the neocortex. To better understand the dynamics of the LE/EP time period, we have employed a method of cell barcoding known as pbCellTag. This method uses a piggyBac transposon system to label cells with unique identifier barcode sequences. During pbCellTag, plasmids containing unique identifier barcodes downstream of EGFP are electroplated into ventricular cells along with a piggyBac transposase plasmid. Combined with fluorescence-activated cell sorting (FACS) and single cell RNA sequencing (scRNA-seq) techniques, these barcodes can be used to perform lineage tracing at the clonal level to generate insights about the spatial-temporal patterns governing LE/EP cell fate transitions. Here we perform in utero electroporation specifically targeting cortical RG cells and their progeny at E14, collected them during the early postnatal period at P4 using FACS and performed scRNA-seq. Using this approach, we demonstrate that cortical RG cells contribute heavily to the formation of the olfactory bulb, as the majority of cortical RG progeny are fated to become olfactory inhibitory interneurons. Similarly, clones with divergent identities were observed within the dataset indicating that cortical RG cells have tripotent potential.

P3-A-526: Investigating the effect of 16p11.2 haploinsufficiency on astroglial metabolism

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Maintaining homeostatic metabolism is essential for proper brain maturation. Recent research from our lab found abnormal brain metabolism and vascular dysfunction during critical periods of development in a mouse model of 16p11.2 deletion syndrome (16pDel). However, the role of glial cells, central to brain metabolism, in 16pDel remains unknown. To investigate the metabolic state of astrocytes in this syndrome, we assessed abundance of metabolites in primary astrocytes from 16pDel and WT mice. Primary astrocytes were extracted at postnatal day (P)8, allowing for sufficient cellular maturity while minimizing stress during extraction. Astrocytes were cultured to appropriate confluence before intracellular metabolites were extracted for quantification by liquid chromatography-mass spec (LC-MS). Our pilot study in 16pDel astrocytes indicates a reduction in carnosine (mitochondrial function), as well

as in glyceric acid (glycolysis intermediate), and in adenosine compared to WT astrocytes. We also measured increased fructose 1,6-biphosphate (converted glucose), fructose 6-phosphate and erythrose 4-phosphate (Calvin cycle intermediates) in 16pDel astrocytes. These preliminary findings indicate a metabolic change in these cells. This will be repeated in astrocytes induced from human pluripotent stem cells obtained from control individuals and 16p11.2 deletion carriers. Overall, this project will identify functional and metabolic alterations in astrocytes, pinpointing to disrupted energetic pathways and unveiling mechanisms of astrocyte dysfunction in autism spectrum disorders.

P3-A-527: Examining the function of Teneurin-3 and Latrophilin-2 in the development of spinal sensory afferent somatotopy

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Somatotopy is a recurring organisational principle within the central nervous system where neurons and their connections are arranged according to the layout of the body. Somatotopic maps have been most famously shown to exist within the primary somatosensory cortex but are also present throughout all levels of the somatosensory system -- including the dorsal horn of the spinal cord. Primary sensory afferents that correspond to the distal limb project medially within the dorsal horn while those that correspond to proximal regions of the body project more laterally. This organisation is also reflected in the response properties of many dorsal horn neurons. How this somatotopic organisation develops remains poorly understood. Our lab has recently identified complementary mediolateral gradients of Teneurin-3 (Ten3) and Latrophilin-2 (Lphn2) within the dorsal horn that correspond to its somatotopic layout. We also observe corresponding expression patterns in the primary sensory neurons of the dorsal root ganglia. Heterophilic repulsion mediated by these proteins has recently been shown to guide the wiring of hippocampal circuits during development. Our current work examines the requirement of these two proteins for the organisation of primary sensory afferents in the dorsal horn. Our preliminary results demonstrate that Ten3 is required for the ability to localise a nociceptive stimulus along the proximodistal axis. Preliminary data also suggests this mechanism might be conserved at higher level targets within ascending somatosensory pathways.

P3-A-528: Loss of Rai1 enhances hippocampal excitability and epileptogenesis in mouse models of Smith-Magenis syndrome

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Hyperexcitability of brain circuits is a common feature of autism spectrum disorders (ASDs). Genetic deletion of a chromatin-binding protein,retinoic acid induced 1 (RAI1), causes Smith-Magenis syndrome (SMS). SMS is a syndromic ASD associated with intellectual disability, autistic features, maladaptive behaviors, overt seizures, and abnormal electroencephalogram (EEG) patterns. The molecular and neural mechanisms underlying abnormal brain activity in SMS remain unclear. Here we show that panneural Rai1 deletions in mice result in increased seizure susceptibility and prolonged hippocampal duration in vivo and increased dentate gyrus population spikes ex vivo. Brain-wide mapping of neuronal activity pinpointed selective cell types within the limbic system, including the hippocampal dentate gyrus granule cells (dGCs) that are hyperactivated by chemoconvulsant administration or sensory experience in Rai1-deficient brains. Deletion of Rai1 from glutamatergic neurons, but not from gamma-aminobutyric acidergic (GABAergic) neurons, was responsible for increased seizure susceptibility. Deleting Rai1 from the Emx1Cre-lineage glutamatergic neurons resulted in abnormal dGC properties, including increased excitatory synaptic transmission and increased intrinsic excitability. Our work uncovers the mechanism of neuronal hyperexcitability in SMS by identifying Rai1 as a negative regulator of dGC intrinsic and synaptic excitability.

P3-A-529: Prenatal EtOH and THC exposure alters interneurons and microglia in the hippocampus of adult rats

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Prenatal cannabis (THC) and alcohol (EtOH) co-use is a growing health concern. Prenatal alcohol exposure (PAE) causes a continuum of disabilities, including learning and memory deficits. Prenatal cannabis exposure (PCE) also affects neurodevelopment and memory but the impact of EtOH+THC remains elusive. The hippocampus is a shared target for EtOH and THC, and represents a potential convergence point for PAE+PCE. Parvalbumin (PV) and somatostatin (SOM) interneurons play an integral role in hippocampal memory, suggesting sensitivity to EtOH and THC. These teratogens also impact neuroinflammation, thereby implicating hippocampal microglia. This study examined the effect of PAE and/or PCE on hippocampal interneurons and microglia in the offspring brain. Pregnant Sprague-Dawley rats were treated with 1) vehicle control, 2) 95% EtOH, 3) THC or 4) 95% EtOH+THC between GD5-20. PV+ and SOM+ interneurons were quantified using immunohistochemistry. In offspring (PND60-70) PAE and PAE+PCE increased PV+ cells in the dorsal CA1, while PAE reduced SOM+ cells in the CA1. Further, PCE decreased PV+ cells in the ventral dentate gyrus (DG) of males but not females. Microglia were identified as Iba1+ cells and morphologically was classified based on circularity. PCE reduced the circularity of Iba1+ cells in the dorsal DG and ventral CA1 in both males and females. In contrast, circularity was decreased in the dorsal CA1 in females only. This study demonstrates that EtOH and THC, when used alone vs. in combination, leads to distinct cellular changes, which are sexually dimorphic.

P3-A-530: Uncovering striatal dopamine circuit development and social behaviour modulation in a mouse model of autism spectrum disorder

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Autism Spectrum disorder (ASD) is a diverse neurodevelopmental condition which affects approximately 1 in 100 children worldwide. Despite being diverse, there are certain behaviours which 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. We are using intersectional genetics to investigate the neurobiological basis of ASD by mapping DA circuits in the striatum at critical developmental timepoints in a mouse model of ASD (Shank3B mutant mice). We are using mice that express Cre and Flp recombinases to control the expression of synaptophysin-GFP (Syn-GFP) specifically in DA neurons. Since synaptophysin is located on neurotransmitter vesicles, the expression of Syn-GFP allows us to visualize DA release sites in the developing striatum using confocal microscopy. Here we present data on DA circuit development in the striatum of early-postnatal Shank3B mutant mice, highlighting the usefulness of this intersectional genetic technique for its specificity and expression at early timepoints. In addition, we are currently investigating the activity of DA circuits in the ventral striatum of Shank3B mutant mice during social behaviour using in vivo calcium imaging. We hypothesize that DA synaptic development is altered in the ventral striatum in Shank3B mutant mice compared to wildtype mice, contributing to 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-531: The ubiquitin ligase and scaffold MYCBP2 is required for EphB2 signalling

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Eph receptor tyrosine kinases play important roles in diverse physiological processes. Whereas the mechanisms governing the magnitude, duration, and termination of Eph receptor signalling, are still mostly elusive. We performed AP-MS to characterize the EphB2 interactome and identified MYCBP2, an E3 ubiquitin ligase and scaffold protein. We demonstrated that EphB2-MYCBP2 interaction is facilitated by FBXO45 and expressing the FBXO45 binding domain of MYCBP2 (FBD1) disrupts the EphB2-MYCBP2 interaction. Moreover, MYCBP2 knockout cells exhibited a reduced ephrin-B2-evoked cell retraction and ephrin-B2 avoidance. Similarly, reduced ephrin-B2 avoidance was observed in cultured cells and chick spinal cord explants expressing the FBD1 fragment. In addition, FBD1 overexpression also impaired ephrin-B ligand-induced hippocampal neuron growth cone collapse. In HeLa cells, MYCBP2 loss-of-function resulted in decreased EphB2 expression levels, indicating that MYCBP2 increases EphB2 stability. Intriguingly, MYCBP2 loss also leads to Kinase Dead EphB2 degradation after ligand treatment, suggesting that its protective role is not dependent on EphB2 kinase activity. Moreover, EphB2-mediated

pERK1/2 activation is impaired in MYCBP2 knockout cells. Literature and our current experiments suggested that MYCBP2 may stabilize EphB2 by regulating the ubiquitination levels of EphB2 and the autophagy levels in cells. MYCBP2 is thus a key effector of EphB2 signalling. A recent study showed that EphB2 induces the levels of c-MYC by inhibiting MYCBP2's activity through its direct interaction with MYCBP2. Our work raises the possibility that MYCBP2's regulation of the EphB2 signalling cascade allows this pathway to reciprocally control the activities of both EphB2 and MYCBP2.

P3-A-532: Characterization of the mechanisms underlying the exuberant axonal development of dopamine neurons.

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Dopamine (DA) neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) are known to have highly developed axonal arborization and a much higher number of axonal terminals compared to most other types of neurons. However, the cellular and molecular mechanisms underlying the development of such morphological features are unknown. The main objective of this project is to better understand the development of the axonal arborization of mouse DA neurons and the mechanisms involved. Our main hypothesis is that DA neurons develop an unusually large axonal arbor either because their growth kinetics are faster or because they continue growing for a longer period compared to other neurons. To tackle this question, we are using timelapse confocal microscopy and primary DA neurons obtained from transgenic mice expressing the fluorescent protein TdTomato selectively in DA neurons or glutamatergic neurons of the thalamus. Our results reveal that there is no significant difference in the rate of axonal growth within the first 24h when comparing SNc DA neurons to VTA DA neurons or glutamate neurons. However, preliminary data obtained at 3 DIV suggest that at this stage SNc DA neurons tend to have higher axonal arborization size compared to the other groups, suggesting that a key stage of axonal development occurs at this time point. We are presently finalizing a more complete comparison of axon growth at 3 and 7 DIV. This project will provide a better understanding of the development of DA neurons, which could ultimately help to better understand their vulnerability in Parkinson's disease.

P3-A-533: Hidden Markov Modelling of neural activity supporting language in development

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The language network is bilateral in childhood and lateralizes leftward across development. To examine the relationship between developmental lateralization and language network dynamics, we used Hidden Markov Models (HMMs) on magnetoencephalographic source waveforms in 79 children and adolescents (ages 4 to 18 years old) performing verb generation. We estimated HMMs ranging from two to ten states. Variance of occupancy across states was lowest for the 5-state model, which had a task-positive state with probability of instantiation rapidly peaking at 100 ms post-stimulus, followed with a late wave

of occupancy from 550-2000 ms. State occupancy and dwell time increased with age. Power was suprathreshold in the delta/theta (1-7) frequencies. Delta/theta power contributions to the observation model was bilateral for young children, and increasingly left lateralized with age. Coherence network remained relatively bilateral across age groups. Laterality indices (LIs) were estimated based on state delta/theta power, and low-beta (13-23Hz) event-related desynchrony, which is an established signature of language network engagement. Increasing leftward laterality with age was associated with prolonged dwell times and occupancy of language state. Results suggest that increasing maintenance (and possibly efficiency) of transient neuronal coordination may underly language network development.

P3-A-534: Deletion of adaptor protein p66ShcA enhances neural stem cell survival in the absence of EGF and ERK signalling

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Neural stem cells (NSCs) rely on cues from their extracellular environment to mediate their survival and maturation. The Shc adaptor family facilitates trophic factor signalling by providing intracellular scaffolds for protein-protein interactions. A member of this family, p66ShcA, however, antagonizes mitogenic signalling and instead promotes apoptosis. Though p66ShcA is strongly expressed in NSCs, and tightly regulated during brain development, its involvement in NSC apoptosis has not been explored. To evaluate p66ShcA's role in the fate of NSCs, we generated and characterized a p66ShcA-null murine NSC line (p66KO-NSC). The NSCs were characterized by assessing their differentiation competency and viability in response to alterations in epidermal growth factor (EGF) signalling. The withdrawal of EGF caused the death of the WT NSCs but had a negligible effect on the survival of the p66KO-NSCs. Moreover, the pharmacologic inhibition of EGFR recapitulated this finding, inducing the death of the WT NSCs without affecting the viability of the p66KO-NSCs. Using pharmacologic inhibitors downstream of the EGFR signaling, we discovered that this could further be recapitulated by the inhibition of ERK, but not by the inhibition of PI3K. The inhibition of either EGFR or ERK induced WT NSC apoptosis via the release of cytochrome C and caspase-3 activation. Remarkably, the p66KO-NSCs were insensitive the EGFR/ERK-inhibition mediated apoptosis, which instead promoted their neuronal differentiation. These findings identify a novel role of p66ShcA in initiating NSC apoptosis in response to the loss of mitogenic cues. This work contributes to understanding the intracellular mechanisms that mediate NSC apoptosis, and to how these pathways intersect with ERK to govern NSC fate.

P3-A-535: Neurogenesis in the developing hippocampus is modulated by vesicular zinc, sex, and age

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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 signalling and modulation. Vesicular zinc-focused research has mainly been directed to its role in the hippocampus and its role in adult neurogenesis. However, whether vesicular zinc is involved in modulating neurogenesis during the early

postnatal period has been less studied. To elucidate 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 at three different age points spanning postnatal development (postnatal day [P] 6, 14, 28). The survival and neuronal differentiation of these cells was also assessed in adulthood (P60). We found that male ZnT3 KO mice displayed lower cell proliferation at P14, but 91% of these cells survived to P60, suggesting loss of vesicular zinc may alter normal cell proliferation and cell pruning at this age. We also found sex-dependent differences whereby male mice had higher levels of cell proliferation at P28 and higher levels of cell survival for P14-labelled cells, compared to females. However, more P14-labelled cells survived to become neurons in females. Finally, we found significant effects of age of BrdU injections on cell proliferation, survival, and differentiation. Our findings offer novel insight into how vesicular zinc modulates hippocampal neurogenesis during early postnatal development and highlight prominent sex- and age-dependent differences.

P3-A-536: Within-person variations in cannabis use and cortical thickness in a longitudinal adolescent cohort

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Adolescent exposure to cannabis is associated with increased risks for adverse outcomes including psychotic disorders; however, the impact of adolescent cannabis exposure on brain maturation is poorly understood. During adolescence, cortical grey matter volume declines until early adulthood primarily attributed to reductions in cortical thickness. Cross-sectional studies can test the impact of between- but not within-person variations in cannabis use on the brain. Participants (n=149) drawn from a population-based longitudinal cohort (n>3800 youth) completed T1-weighted MRI scans at 13, 15, and 17 years old. To investigate the distinct contributions of between- and within-person variations in cannabis use on brain structure, cannabis use was split into between-person and within-person variables. At time points when male participants reported greater cannabis use, their cortical thickness was lower-than-expected considering age and controlling for alcohol or tobacco use ($p<.005$). This effect was not observed in female participants ($p>.05$) and was not observed if cortical surface area was the outcome measure ($p>.05$). This effect in males did not differ across brain regions (interaction: $p>.5$). In contrast, average cannabis use was not associated with cortical thickness across the cohort ($p>.05$). This preliminary analysis provides evidence relating within-person increases in cannabis use to greater-than-expected cortical thinning in male adolescents and highlights advantages of longitudinal design and analytic approaches that separate between- and within-person effects.

P3-A-538: Inverse correlation between the human umbilical cord sympathetic innervation and clinical variables of newborns prenatally exposed to cocaine

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Prenatal cocaine exposure alters sympathetic innervation of umbilical vessels and compromises maternal-filial blood flow. However, the molecular mechanism underlying the change in umbilical cord sympathetic innervation is unknown. Since umbilical cord (UC) expresses semaphorin-3A (Sema3A), a repulsive axon-guidance molecule, we hypothesize that Sema3A underlies the inverse correlation between a newborn's clinical manifestations due to maternal cocaine use and the perivascular sympathetic innervation of the umbilical cord. We evaluated perinatal clinical histories of UC donors and correlated them with the innervation of the UC. Immunofluorescence assays were used to measure the expression of Sema3A in UC sections, and we conducted co-labeling experiments with anti-TH, a specific marker for sympathetic fibers, to evaluate the association between sympathetic innervation and Sema3A protein expression. Prenatal exposure to cocaine resulted in a decrease in body weight, head circumference, and gestational age, whereas, there was no difference in age or body-mass-index among mothers. We found a negative correlation between sympathetic innervation of umbilical arteries and a newborn's body weight, size and head circumference. Moreover, we expect a negative correlation between Sema3A expression in umbilical cords and sympathetic innervation. Our results reveal a potential mechanism underlying developmental disorders and prenatal cocaine exposure. Differences in Sema3A expression could prove a molecular mechanism for changes in sympathetic innervation induced by cocaine.

P3-A-539: Synapse formation: contributions of the GPR55 receptor

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Recent studies have demonstrated the important role of the endocannabinoid system in the development of the central nervous system, notably through the presence of the GPR55 receptor and the impact of its modulation in the growth and guidance of axons during the fetal and perinatal periods. Since some molecules and cellular mechanisms involved in these processes may also play a role in synaptogenesis, the objective of the present study is to determine the involvement of GPR55 and the impact of its modulation in the formation of synaptic contacts. For this purpose, mouse embryo cortices from wild-type and gpr55KO were isolated and cortical neurons dissociated. We studied the effects of GPR55 deletion in synaptic contact formation at different days in vitro (DIV) and its pharmacological modulation by exposing neurons with a GPR55 antagonist, cannabidiol (CBD), or an agonist, lysophosphatidylinositol (LPI). These effects were studied by immunocytochemistry, immunoblot and patch clamp electrophysiology. The results show that GPR55 is involved in synaptic maturation and that its deletion leads to a decrease in the synaptic activity of cortical neurons. Moreover, CBD and LPI could influence the formation of synaptic contacts in a GPR55-dependent manner. The understanding of synaptic formation mechanisms will improve our knowledge in the fields related to the development of the central nervous system. From a public health perspective, understanding the impact of CBD modulation of GPR55 on synaptic contact formation will increase awareness of the effects of perinatal CBD use.

P3-A-540: Control of CREB-dependent gene expression by store-operated calcium entry in iPSC-derived human neural progenitor cells.

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cAMP Response Element-Binding Protein (CREB) is a transcription factor implicated in many neuronal processes. CREB becomes active when it is phosphorylated at serine 133 by different kinases downstream of Ca2 -dependent signaling pathways. In neural progenitor cells (NPCs), intracellular Ca2 level is primarily regulated by storage-operated Ca2 entry (SOCE)--a mechanism that promotes Ca2 influx through ORAI channels when Ca2 stored in the endoplasmic reticulum is released. Evidence shows that SOCE contributes to the proliferation and differentiation at the NPC stage of neurodevelopment. Interestingly, no direct connection has been made between SOCE and CREB activity in those cells to date. Therefore, we tested whether CREB phosphorylation is influenced by SOCE-facilitated Ca2 influx and seek to understand how this interaction could affect downstream gene expression using human induced pluripotent stem cell (iPSC)-derived NPCs. Indeed, our results suggest that SOCE activation rapidly promotes the phosphorylation of CREB as well as significant changes in gene expression. Intriguingly, testing with pharmacological inhibitors suggest that CREB phosphorylation may be separate from the known CREB-activating pathways in neurons, namely PKA, MAPK/ERK, CAMKII/IV, and PI3K/AKT. Finally, an RNA-sequencing analysis revealed that SOCE activity upregulated a distinct set of neurodevelopment-related genes. Taken together, these findings provide a better understanding of the role SOCE-dependent CREB activation plays in the early stages of neuron growth and differentiation.

P3-A-542: Ikzf2 regulates amacrine cell diversification in the developing mouse retina

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During Central Nervous System development, neural progenitors generate different cell types in a strict chronological order, and any perturbance in this birth order impairs the development of functional circuits. But how exactly cell birth order is regulated at the molecular level remains poorly understood. The vertebrate retina is a good model system to address that question, as multipotent retinal progenitor cells (RPCs) give rise to retinal cell types in a precise chronological order that is conserved between different vertebrate species. Previous work in our lab identified the zinc finger transcription factor (TF) Ikaros1 (Ikzf1) as a key regulator of temporal identity progression in the retina, but partial phenotypes in loss of function experiments suggest that other factors are also involved. Here, we investigated the role of the TF Ikzf2 during retinogenesis. We report that misexpression of Ikzf2 in late-stage RPCs promotes the heterochronic generation of Pax6 and Prox1-positive amacrine cells (AC), an early-born cell type. Conversely, inactivation of Ikzf2 in vivo leads to a reduction in the number of AC observed in a mature retina. Finally, gene expression profiling of Ikzf2 overexpressing RPCs shows that non-Glycinergic and non-GABAergic AC fate is favoured in presence of Ikzf2. These results suggest that Ikzf2 regulates a gene

regulatory network in RPC leading to the timely production of specific subtypes of ACs. This work may allow the development of new protocols to stimulate neurogenesis from different sources, potentially contributing to retinal repair and neuronal replacement strategies.

P3-A-543: Altered GABAA receptor configuration associated with cortical dysmaturity in cortical dysplasia

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Introduction: Focal cortical dysplasia (FCD), developmental disorder of cerebral cortex, is the most common form of drug-refractory epilepsy in pediatric patients. Dysmaturity hypothesis suggests that interactions of dysmature cells with normal neurons promote seizures in FCD. Previous studies suggested that altered GABAA-receptor configuration with higher alpha4 expression in FCD as observed in immature brain during development. In this study, we are investigating the role of GABAA alpha4 subunit in pathophysiology of FCD by correlating its expression with clinical parameters. Methods: FCD (n=15) and autopsy (n=10) samples as well as FCD-rat model were used in this study. Real-time PCR and western blotting analysis was carried out to check GABAA receptor alpha4 and 1 mRNA and protein expression. Results: An increase in mRNA as well as protein expression of alpha4 subunit was observed in human and rat FCD samples with no significant change in alpha1 expression in FCD compared to autopsy and control rat samples. Further analysis show higher alpha4/1 ratio in FCD wrt control. On correlation with clinical parameters, higher alpha4/1 ratio was observed in early onset and higher seizure frequency patients compared to late onset and low seizure frequency patients respectively. Conclusion: This study highlights the alteration in GABAA receptor configuration in FCD with higher alpha4/1 ratio compared to control samples. Our study further confirms direct correlation of increased alpha4/1 ratio with early onset and high seizure frequency. This study suggest GABAA receptor alpha4 subunit could be used as a pharmacological target for FCD treatment.

P3-B-545: Investigating mesencephalic astrocyte-derived neurotrophic factor (MANF) in ketamine mediated endoplasmic reticulum stress

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There is major concern over the increased use of ketamine in recreational and therapeutic settings due to its neurotoxic effects. Long-term ketamine use is associated with neurodegeneration in humans, rodents, and non-human primates, including loss of grey matter that correlates with severity and duration of use. Recent work has established endoplasmic reticulum (ER) stress as a mechanism underlying ketamine neurotoxicity. MANF is an ER-resident protein that plays a critical role in maintaining and restoring ER homeostasis by attenuating stress. Thus, we aimed to investigate the neuroprotective role of MANF in ketamine-mediated neurotoxicity. To investigate the role of MANF, we generated CRISPR/Cas9 MANF-knockout (KO) mouse striatal cells and examined the effects of MANF deficiency on ketamine-induced cell death. To test whether MANF is neuroprotective, mouse striatal cells

were treated with ketamine (100uM, 1mM) with or without 100ng recombinant human MANF protein for 24 hrs. Cell viability was quantified by MTT and PrestoBlue assays. Results showed MANF deficiency exacerbated ketamine-induced cell death in a dose-dependent manner, with increased vulnerability observed at 10uM and 100uM in MANF-KO cells. Treatment with MANF protein was not protective against ketamine-induced cell death and exacerbated death caused by ketamine. These results demonstrate that concurrent MANF treatment is not neuroprotective against ketamine neurotoxicity. Different treatment regimens are needed to further explore the therapeutic potential of MANF in ketamine neurotoxicity and ER stress.

P3-B-546: 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 activated 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. 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 promotes the differentiation of OPCs to mature oligodendrocytes in CSPGs matrices. Microglia plated on CSPGs matrix induces the breakdown of CSPGs by inducing the release of MMP 9 and MMP 2 and the treatment of PTN the presence of CSPGs induces the release of IL6, MCP1, IL 10 and TNF A 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-B-547: Potential of Cannflavins A and B to Limit Glioblastoma Invasion and Survival

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Cannflavins A and B are cannabis-enriched flavonoids known to reduce inflammation via biosynthesis inhibition of pro-inflammatory mediators. Accumulating evidence also suggests that these prenylated flavones may have neuroprotective and anti-cancer properties, but the mechanisms responsible for

these effects remain elusive. While screening for novel modulators of receptor tyrosine kinases in neurons, our group found that cannflavins A and B can prevent Tropomyosin receptor kinase B (TrkB) receptor activation by growth factor BDNF. Since signaling by TrkB is a major factor in the biology of various types of brain tumors, and that targeting this pathway may be an effective strategy to limit the growth of aggressive cells, we aimed to test whether cannflavins can be leveraged to affect the survival, proliferation, and migration of glioblastomas (GBMs). Here, we used U87 and A172 GBM lines to conduct cell viability, migration, and invasion assays. Cannflavins A and B, along with a known TrkB inhibitor ANA-12, produce significant effects at a minimal dose against the tested hallmarks of cancer. Our study represents an initial effort to complete a systematic preclinical characterization of cannflavins against GBMs. Our goal is to position cannflavins as candidate therapeutic molecules to attack brain tumors, as well as other cancer types that thrive on the aberrant activity of TrkB.

P3-B-548: Developmental defects in nanoscale reorganization of AMPARs and quantal transmission in a mouse model of fragile X syndrome

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Excitatory synapses undergo rapid remodeling during early sensory development by changing the abundance, composition, and nano-organization of postsynaptic glutamate receptors to enable neurotransmission. Dysregulation of synaptic remodeling can lead to neurodevelopmental disorders such as fragile X syndrome (FXS), caused by a mutation in the Fmr1 gene encoding FMRP. It is unknown how FMRP deletion impacts the nano-organization of AMPARs and quantal transmission during early synaptic development. Using the calyx of Held synapse in the auditory brainstem, where AMPARs undergo a developmental subunit switch from slow-gating GluA1- to fast-gating GluA4-dominant, we applied expansion (ExM) and STED microscopy to map nanoscale differences in subsynaptic localization of GluA1- and GluA4-AMPARs between wild-type (WT) and Fmr1-/- mice at pre- (P8-10) and post-hearing (P16-19) stages. We see partially mismatched GluA1- and GluA4-AMPAR nanodomains, supporting the bimodal distribution of fast and slow mEPSCs in WT mice, which is altered in Fmr1-/- synapses. The bimodal distribution of fast and slow mEPSCs in immature Fmr1-/- synapses phenocopies that of mature WT synapses. Basal mEPSC frequency was significantly higher, and less sensitive to an elevation of extracellular Ca2+ in Fmr1-/- synapses, indicating altered presynaptic remodeling. Our study suggests loss of FMRP accelerates developmental remodeling of both pre- and postsynaptic elements underlying quantal transmission, implicating the critical role of FMRP in controlling the pace of activity-dependent synaptic maturation.

P3-B-549: Sex differences in astrocyte neuronal metabolic coupling during chronic inflammatory pain in the anterior cingulate cortex of mice

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Up to 25% of Canadians suffer from chronic pain, and Women make up 67% of this group. Treatment remains inadequate, and new molecular targets to improve treatment efficacy are needed. Chronic inflammatory pain corresponds with neuroplasticity of the anterior cingulate cortex (ACC), including increases in immediate early genes and excitatory transmission. These processes impose a large and rapid energy demand. In the present study, we used a mouse model of chronic inflammatory pain, Complete Freund's Adjuvant, to determine if astrocytes provide this energy via astrocyte-neuronal lactate shuttling (ANLS).. Activation of the ANLS was examined through both measurement of lactate levels and monocarboxylate transporter 4 (MCT4)and MCT2, which bidirectionally transport lactate across astrocytes and neurons, respectively. Measures of behavioural pain thresholds, Lactate, and MCT4 levels were taken at 3h, 24h, 3d and 7d following injection. We found that ANLS was activated by persistent inflammatory pain in a sex dependent manner. Although both sexes showed a rapid, significant increase in lactate levels in the ACC at early timepoints, only male mice showed significant levels seven days following injection, compared to controls. Similarly, ACC samples from female and male mice showed increases in MCT4 protein expression at early time points following CFA injection, but only males showed increased levels seven days following injection. Our data indicates that chronic inflammatory pain engages ANLS in the ACC in a sex specific manner.

P3-B-550: Role of radial astrocytes on the encoding of visual signals and plasticity in the developing xenopus laevis optic tectum.

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During late stages of brain development, efficient circuit wiring relies on instructive cues from sensory experience and neural activity to drive synaptic plasticity and achieve mature functional connectivity. Initially thought to only implicate neurons, recently glia have been shown to be involved in the neural plasticity mechanisms that mediate structural and functional circuit refinement. Given that glia ramify within brain regions, providing guidance and structural support for neurons, do they play a role in tuning their functional properties as well? Using the visual system of Xenopus laevis we conducted live 2-photon calcium imaging while presenting visual stimuli to study the role of radial glial activation in neural plasticity. To selectively control the activity state of radial glia of the tectum they were transfected with mutant TrpV1 channels that act as chemogenetic targets. We observed only a small number of cells responding to the visual stimuli, which is consistent with previous findings of sparse information encoding. Glial activation increased the strength and duration of short- and long-term depression after plasticity-inducing stimuli. On the other hand, the activity within the neuropil, where retinal ganglion axons synapse onto tectal neurons, saw a significant increase in responsiveness to the stimuli after induction and glial activation, in contrast to the control group in which glia were not activated. Our results indicate that glial activation differentially modulates the synaptic and somatic responses to modulate signal transduction and plasticity.

P3-B-551: The Impact of Adolescent Repeated Mild Traumatic Brain Injuries on MS-Like Pathology

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Mild Traumatic Brain Injuries (mTBIs) account for ~80% of TBIs and are prevalent in adolescents. Recent retrospective studies have shown a link between multiple sclerosis (MS) development and adolescent mTBIs. However, the cellular and molecular mechanisms underlying this phenomenon are unknown. Our group uses a lateral impact model of repeated mild traumatic brain injury(RmTBI). Using this model, we have shown sex and time-dependent behavioural deficits and neuroinflammatory responses in adolescent mice. We hypothesized such neuroinflammatory responses following RmTBI could initiate a cascade of events that exacerbate MS pathology and prime microglia to take on a chronic proinflammatory phenotype. We gave adolescent mice of both sexes RmTBIs or sham injuries. Following the last injury, mice were assessed on the rotarod motor assay and received a diet of 0.2% cuprizone (CPZ) for 2-weeks. Cuprizone is a demyelinating agent, and we hypothesized that mice that received RmTBIs prior to cuprizone would display a worse behavioural and neuroinflammatory phenotype compared to shams. We performed the same behavioural tasks prior to sacrificing the mice. We assessed the extent of gliosis and demyelination using immunohistochemistry. Mice of both sexes subjected to RmTBIs had persistent behavioural deficits on rotarod and an exacerbation of demyelination following CPZ in the cerebral peduncles. Upon further study we found the motor deficits seen were driven by the injuries themselves, irrespective of 2-weeks of CPZ feeding. It might be that we are missing the effects of RmTBI on CPZ-induced motor deficits. Therefore, we will investigate the influence of RmTBIs on 4-weeks of cuprizone feeding to investigate a feeding period with more pronounced motor deficits and demyelination.

P3-B-552: Golgi-Cox staining reveals altered apical, basal dendrites and spine density of pilocarpine model of temporal lobe epilepsy (TLE)

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Introduction: Temporal lobe epilepsy (TLE) is a distributed network disorder, which involves the hippocampus and extra-hippocampal structures. Epileptogenesis in temporal lobe epilepsy (TLE) is tightly associated with neurogenesis, plastic changes and neural network reorganization. In the present study, we investigated using Golgi impregnation, tiny neuronal architecture of pyramidal neurons in the in the hippocampus, anterior temporal lobe (ATL) and neocortex at the dendritic and spine levels Methods: Li-Pilocarpine was used to induce a status epilepticus (SE) in S. D. rats. Golgi-Cox staining was achieved according to standard protocol to visualize neurons in their cell soma(cell body), axons, dendrites, and spines. In brief, rats were transcardially perfused with 0.9% of saline (PBS) followed by 4% PFA. Later the perfusion, brains were dissected out and fixed in Golgi solution for 48 hrs. The brain sectioning was performed using vibratome into 200-µm slices, onto gelatin-coated slides. The slides were dehydrated at room temperature and further followed by alcohols gradient decreasing order series for dehydration. Golgi-Cox stained pyramidal neurons of hippocampal (CA1), 5th layer pyramidal neurons of

ATL, and neocortex of TLE and control rats sections were observed under a microscope (Olympus BX50) and analyzed using Neurolucida software (MBF Bioscience). Dendritic morphology was analyzed by using a 40× objective lens. Results: The length of apical and basal dendrites, spine density and soma architecture were altered in pilocarpine rat model of epilepsy (TLE). Sholl analysis revealed a significant increase spine density, length of the apical and basal dendrite in TLE treated rats compared to control rats. We also observed increased intersections in the ATL region of

P3-B-553: The spatial separation of voltage-gated sodium channel subtypes in the axon initial segment can have opposite effects on backpropagation depending on the site of stimulation

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In a variety of neurons, action potentials (APs) initiate at the proximal axon, within a region called the axon initial segment (AIS), which has a high density of voltage-gated sodium channels (Navs) on its membrane. In pyramidal neurons, the proximal AIS has been reported to exhibit a higher proportion of Navs with gating properties that are "right-shifted" to more depolarized voltages, compared to the distal AIS. Further, recent experiments have revealed that as neurons develop, the spatial distribution of Nav subtypes along the AIS can change substantially, suggesting that neurons tune their excitability by modifying said distribution. When neurons are stimulated axonally, computational modelling has shown that this spatial separation of gating properties in the AIS enhances the backpropagation of APs into the dendrites. In contrast, in the more natural scenario of somatic stimulation, our simulations show that the same distribution impedes backpropagation. We implemented a range of hypothetical Nav distributions in the AIS of a multicompartmental pyramidal cell model and investigated the precise kinetic mechanisms underlying such effects, as the spatial distribution of Nav subtypes is varied. With axonal stimulation, proximal Nav availability dominates, such that concentrating right-shifted Navs in the proximal AIS promotes backpropagation. However, with somatodendritic stimulation, the model is insensitive to availability. Instead, the higher activation threshold of right-shifted Navs in the AIS raises the neuron's backpropagation threshold. The effects on backpropagation, and potentially learning, are opposite for orthodromic versus antidromic stimulation.

P3-B-554: Linking mRNA levels from patch-seq experiment to surface conductance density values of ion channel in electrophysiological models of cortical neurons.

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Functional features of neurons are expected to emerge from the genes they express. Recent multimodal cellular datasets providing both electrophysiological and transcriptomic information of neurons have been used to explore putative links between gene expression profiles and cells electrical functionalities. However, clear rules appears difficult to delineate. Here we propose an improved methodology by adding an intermediate modelling step before exploring such links. Inspired from previous works available in the literature, we built detailed morpho-electrical models of neurons from an adult mouse Patchseq dataset. Additionally, we took advantage of the recently developed genetic ion channel models from Channelpedia. As a result, we obtained a collection of models that had the same morphologies and comparable electrophysiological behaviour to the biological samples. In addition, these models had conductance densities of ion channels that were directly relatable to genes (e.g Kv3.1 to Kcnc1). We then exploited these optimised genetic ion channels densities to relate them to the gene expression profiles. A fine grained analysis at the sample level yielded no clear correlations while agglomerating RNA data with a larger scRNAseq experiment at the transcriptomic type level suggested some trends supported by

the literature. This method shows good potential on providing new insights on the relations between gene expression and electrophysiological behaviour of cells if given a sufficient number of samples.

P3-B-555: Glutamate transporter blockade induces distinct excitatory currents in melanin-concentrating hormone neurons

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Objective: Positive energy balance and sleep are coordinated by melanin-concentrating hormone (MCH) neurons in the hypothalamus. The excitatory transmitter glutamate (Glu) plays an important role in shaping the activity of MCH neurons, which is regulated by Glu transporters present on astrocytes and neurons. To understand how Glu regulates MCH neurons, we investigated the role of Glu transporters in controlling the extracellular Glu surrounding these neurons. Methods: We performed whole-cell patch clamp recordings of MCH neurons in acute brain slices from MCH-cre tdTomato mice. To investigate the role of Glu transporters, a non-specific Glu transporter blocker TFB-TBOA was used. Results: We identified three kinetically distinct excitatory currents induced by a 5-min application of TBOA: a tonic inward current (TIC) which peaked at 5 min after TBOA application and returned to baseline in 10-15 min, and two types of transient currents, i.e., step currents (time course 20-25 sec) and slow inward currents (SICs, 0.1-14 sec). These currents were mediated by non-NMDA and NMDA receptors and dependent on action potential-dependent release. Furthermore, TIC was largely inhibited by postsynaptic application of MK-801, indicating a role for ionotropic postsynaptic NMDAR. 12-h fasting reduced the amplitude and frequency of TIC and SICs respectively, while step currents were unaffected, suggesting that Glu signaling in MCH neurons and its regulation by Glu transporters are altered under negative energy balance. Conclusion: MCH neurons under the influence of ambient and transient Glu signals are regulated by Glu transporters. These currents are sensitive to fasting, suggesting their physiological role in energy homeostasis. Funded by NSERC

P3-B-556: Investigating how loss of NHE6-Rac1 interaction leads to learning deficits in christianson syndrome

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Christianson syndrome (CS) is a monogenic X-linked neurodevelopmental/neurodegenerative disorder caused by loss-of-function mutations of the SLC9A6 gene, which encodes for the endosomal (Na+, K+)/H+ exchanger 6 (NHE6). Loss of NHE6 leads to overacidification of the endosomal lumen, resulting in the mistrafficking of cargo needed for functional and structural synaptic plasticity at the CA3-CA1 synapse. Growing evidence suggests that disruption of the Rac1, a Rho family GTPase, known to play a central role in cytoskeletal remodeling at glutamatergic synapses during learning signaling pathway contributes to Autism Spectrum Disorder (ASD) and NHE6 has been shown to be down-regulated in ASD. We investigated if Rac1 found normally in NHE6 endosomes is misregulated. Using molecular biology, we have found that Rac1 binds directly to NHE6. Using immunoblotting assays, we found no differences in the total Rac1 protein level in hippocampal slices between the wildtype and CS murine model. Interestingly, after inducing learning in both WT and CS hippocampal slices by ChemLTP, we found an increase in Rac1 protein in spines after Chem LTP, which did not occur in the CS, suggesting a possible

trafficking problem. Immunoblot analysis of the signalling cascade for Rac1 activation after chem LTP revealed p-cofilin level were lower in CS vs WT, suggesting a Rac1 signalling deficit resulting in lack of spine remodelling after LTP. The present study gives insight into learning deficits in CS that could be potentially rescued by modulating Rac1 signalling and trafficking in future studies.

P3-B-557: 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. First, we evaluated GPR120 mRNA expression in DA neurons. Intracellular calcium (Ca2+) mobilization and DA release in TH-GFP+ neurons were monitored before and after treatment with a selective GPR120 agonist (AZ13581837; 0.5-10 µM) using a Ca2+ indicator (Biotracker 609) or a fluorescent dopamine transporter substrate (FFN102), respectively. Downstream signaling of GPR120 was assessed by measuring phosphorylated cAMP-response element binding protein (pCREB), morphological analysis, and using an inhibitor for G-protein. GPR120 mRNA is expressed in midbrain DA neurons in primary culture and slice. Bath perfusion of the GPR120 agonist and PUFAs increased intracellular Ca2+ levels and the releasing of FFN102 in TH-GFP+ neurons. GPR120 agonism also increased pCREB and neuronal arborization in DA neurons, an effect that was absent in GPR120 KO mice. Under the inhibition of Gαq signaling, AZ-induced Ca2+ mobilization and DA release were abolished. These results uncover GPR120 activation as an enhancer of DA tone and neuronal plasticity and suggest that this as may be one mechanism underlying the anxiolytic actions of central GPR120 agonism. NSERC RGPIN-2018-06565

P3-B-558: Investigating microglia-neuron crosstalk by characterizing microglial contamination in human and mouse Patch-seq datasets

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Microglia are dynamic immune cells with diverse functional roles, including the regulation of neuronal excitability. Here, we leveraged the multi-modal Patch-seq method to assess the presence and effects of microglia in the local microenvironment of recorded neurons. We first quantified the amount of microglial transcripts in three Patch-seq datasets of human and mouse neocortical neurons and observed extensive contamination by microglia in each dataset. Variation in microglial contamination was explained foremost by donor identity, especially in human samples, and additionally by neuronal cell type identity in mice. Differential expression testing and gene set enrichment analysis suggest that microglial contamination in Patch-seq is reflective of activated microglia and that these transcriptional signatures are distinct from those captured via single-nucleus RNA-seq. Finally, neurons with greater

observed microglial contamination differed markedly in their electrophysiological characteristics, including lowered input resistances and more depolarized action potential thresholds. Collectively, our results generalize beyond Patch-seq to suggest that activated microglia are likely widely present across brain slice preparations and contribute to neuron- and donor-related electrophysiological variability in vitro.

P3-B-559: Conserved early upregulation of prefrontal cholinergic signalling across different species and models of Alzheimer's disease

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Deficits in attention and executive function occur relatively early in Alzheimer's disease (AD). To interrogate the system most relevant for this cognitive decline, we examine the impact of early AD pathology on the cholinergic excitation of the prefrontal cortex. We take advantage of models of AD in two different species to examine early-disease changes: the TgF344-AD rat model that recapitulates the human trajectory of AD pathology, and a compound transgenic mouse that permits optogenetically-triggered release of endogenous acetylcholine (opto-ACh) in the presence of TgCRND8-AD pathology. In the AD rat, we find a significant, unexpected enhancement of deep-layer pyramidal neuron responses to exogenous acetylcholine. This change is specific to the early-disease state, as it is not observed in younger or older rats. We then use the opto-ACh AD mouse to investigate disease impact on cholinergic synaptic function. Paralleling the AD rat results, the opto-ACh AD mouse shows a significant upregulation of the prefrontal cholinergic response in early-to-mid-disease that is lost in older animals. Since upregulation of cholinergic signalling in AD models of both species is observed before cognitive deficits become overwhelming, we hypothesize that a form of molecular compensation may be at work. We are therefore probing the underlying mechanisms to identify new treatment targets to ameliorate the disruption of attention and executive function in AD.

P3-B-560: Local Field Potential Contributions in Detailed Multicompartment Model

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The projects objective is to explore the components of a multicompartment model and their relevant contributions to local field potential approximations. Using the NEURON modelling environment as well as data from FEM models of tissue conductivity in the brain and different neuron models and synapse models the contribution of different compartments and mechanisms will be compared.

P3-B-561: Determining the in vivo roles of TrkC-PTPσ interaction in synapse development

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Synaptic organizing complexes are trans-synaptic adhesion molecules that can promote pre- and post-synaptic differentiation necessary for normal synapse development. The development of chemical synapses is essential for neuronal function and establishment of neuronal networks to enable the processing of information in the brain. Previously, TrkC-PTPσ interaction was identified as a novel synaptic organizing complex, which through in vitro data was shown to promote excitatory, but not inhibitory, synapse development. The genes coding for TrkC and PTPσ are genetically associated with anxiety disorders and autism respectively. However, it is not well understood how this complex regulates excitatory synapse development in vivo and contributes to cognitive functions. To test this, we have generated a mutant mouse line that completely abolishes TrkC-PTPσ interaction. Using this line, I am working on characterizing the biochemical and structural phenotypes of excitatory synapses in the mutant mice, as well as determine the role of this interaction and its effect on the synapse. Furthermore, using different proteomic approaches, we would like to understand the role of this interaction on the synapse protein network. Finally, I am carrying out behavioural tests to determine the behavioural phenotypes in these mice. My project will shed light on the role of this complex in excitatory synapse development in vivo and how its impairment can lead to cognitive dysfunction, as well as enable the development of novel therapeutic strategies.

P3-B-562: G-protein mediated control of TNFα production in glia

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The pro-inflammatory cytokine Tumor necrosis factor (TNFα) is a major part of the innate immune response, but is also an important regulator of synaptic function. In the central nervous system, TNFα can be released by both astrocytes and microglia. To gain a clear insight into the role of TNFα in the central nervous system, we first need to understand the signaling pathways controlling TNFα production from glia. Here, we seek to characterize G-protein coupled receptor (GPCR) signaling that regulates TNFα production from both types of glia. Using DREADDs-based experiments in rat astrocyte culture and pharmacological experiments in rat microglia culture, we assessed the G-protein mediated changes in TNFα as measured by qPCR. Our results show that Gq-GPCR activation in astrocytes significantly decreased TNFα levels, while Gi-GPCR activation significantly increased TNFα production. In microglia, norepinephrine treatment, acting through beta-adrenergic receptors and adenylyl cyclase, strongly reduced TNFα expression, demonstrating that Gs-GPCR activation negatively regulates TNFα production. Overall, our experiments combined with previous results suggests that both types of glia have similar regulation of TNFα expression: Activating Gq and Gs decrease TNFα levels, whereas activating Gi likely increases TNF production. Altogether, neuromodulators acting through GPCRs can bidirectionally regulate TNFα production in glia.

P3-B-563: Differential changes in the intrinsic properties and synaptic function of auditory cortical neurons of Cntnap2 KO rats derived from different breeding schemes.

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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 alterations in auditory cortex pyramidal neurons of Cntnap2-/- rats derived from heterozygous (Cntnap2+/- x Cntnap2+/-) and homozygous (Cntnap2-/- x Cntnap2-/- and WTxWT) breeding pairs. Whole-cell patch-clamp recordings were conducted in wildtype and Cntnap2-/- adult rats from the two breeding schemes. Changes in measures of intrinsic membrane properties were seen exclusively in adult Cntnap2-/- rats from homozygous breeding, while spontaneous synaptic input differences were only seen in Cntnap2-/- rats from heterozygous breeding. Intrinsic cell properties such as action potential half widths, rheobase, and action-potential firing frequencies were different between homozygous bred wildtype and Cntnap2-/- rats, but there were no differences in the heterozygous bred rats. Furthermore, the Cntnap2-/- rats from heterozygous pairings showed higher spontaneous (sEPSC) and mini excitatory post-synaptic currents (mEPSC) frequencies, with lower sEPSC amplitudes. These results show that intrinsic cell properties and synaptic inputs can be differentially altered in Cntnap2-/- rats depending on the breeding schemes. This indicates how sensitive brain development can be to environmental differences, such as potential differences in prenatal and postnatal environments.

P3-B-564: Pharmacologically distinct NMDA receptor-mediated synaptic depotentiation in the rodent hippocampus

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Persistent increases in synaptic strength, referred to as long-term potentiation (LTP), underlie many types of memory formation. Reflecting the dynamic nature of memory, LTP is susceptible to modification post-induction; however, the molecular mechanisms dictating the direction and magnitude of these subsequent plastic changes remain poorly understood. The NMDA receptor is critically involved in bidirectional alterations in synaptic strength in the hippocampus by recruiting distinct downstream signaling cascades. Using brain slice electrophysiology, we sought to pharmacologically interrogate the precise NMDA receptor-mediated signaling pathways underlying LTP reversal, or depotentiation. Using acute hippocampal slices obtained from male 7-12-week-old C57Bl/6NCrl mice, we first optimized a protocol to obtain long-lasting NMDA receptor dependent LTP and characterized its frequency-dependent modification. We induced LTP at CA3-CA1 synapses by either a spaced or compressed electrical stimulation protocol, followed by a low-frequency stimulation pattern to trigger depotentiation. Our preliminary evidence indicates that mechanistically distinct NMDA receptor antagonists targeting either the glutamate or glycine binding site differentially interfere with the reversal of LTP induced by different stimulation patterns. Ongoing experiments aim to elucidate the precise downstream molecular pathways involved in the broad regulation of synaptic strength to maintain homeostasis and enable memory modification.

P3-B-565: Astrocytic nmda receptors maintain optimal circuit activity and neuronal viability

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Introduction: Astrocytes, a type of glial cell, utilize calcium signaling to regulate nearby neuronal activity. Activation of ionotropic N-methyl-D-aspartate (NMDA) receptors on the surface of astrocytes via glutamate can cause calcium elevations. The mechanism by which this calcium signaling can trigger modulation of nearby neuronal activity remains elusive. We hypothesize that astrocytes sense nearby neuronal activity through astrocytic NMDARs leading to refinement of synaptic strength. Methodology: Astrocyte NMDA receptors were specifically targeted using a novel NMDAR knockdown (KD) construct. In-vivo two photon calcium imaging was performed in NMDAR KD and control mice (C57BL6) to visualize astrocytic and neuronal calcium activity. Texture recognition test was performed to characterize the behavior of NMDA KD mice. Furthermore, immunohistochemistry was done to understand the effects of NMDAR KD on neuronal morphology. Results: Whisker stimulation and electrical stimulation cause reduction in astrocytic calcium activity following astrocytic NMDAR KD. Interestingly, neural adaptation to a long electrical stimulation for NMDAR KD mice was significantly slower when compared to control mice. Behavior tests showed that the experimental group had sensory deficits and could not discriminate a small texture difference. According to the immunohistochemistry results, there was a decrease in the number of neurons in NMDAR KD mice. Conclusion: This project highlights the functional relevance of astrocytic NMDA receptors in calcium signaling. This is relevant for diseases such as schizophrenia where NMDA receptors are poorly activated. By understanding the contribution of these astrocyte receptors to brain circuitry, we can better determine the mechanisms of schizophrenia.

P3-B-566: Assessment of the NMDA glutamate receptors in pathogenesis of schizophrenia using iPSC-derived neuronal model and digital holographic microscopy

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Schizophrenia (SZ) is a serious mental disorder characterized by hallucinations, delusions, and impaired cognitive behavior. However, substantial heterogeneity in the clinical phenotypes makes it complicated to diagnose and treatment of it. Its pathogenesis results from a complex interaction between genetic vulnerability and environmental factors, altering neuronal development. Several genes and proteins associated with neurite growth, neuronal migration, and synaptic development were found to be altered in SZ. However, the processes of neurodifferentiation and functional maturation of neuronal networks are still unexplored. Therefore, generating in vitro cortical neural cultures from iPSCs from SZ patients and controls present a unique opportunity to study the neurodevelopmental component of SZ. Concretely, new cutting edge multimodal optical imaging techniques including digital holographic microscopy are used to accurately study the iPSCs neurodifferentiation process which at some extent recapitulate main steps of in vivo neurodevelopment. The induced pluripotent stem cells (iPSCs) lines were differentiated into cortical neural cells and characterized by flow cytometry, immunostaining, western blot, and patch-clamp techniques. After that, based on DHM, we have successfully developed a

methodology to monitor in a non-invasive manner the activity of NMDA glutamate receptors, during the whole neurodifferentiation process. Indeed, an accumulating body of evidence indicates that NMDA receptors are relevantly involved in the pathogenesis of SZ. This methodology represents the basis for further development of a label-free NMDA essay within human neurons in culture that have the genetic background of the patient from which they were derived.

P3-B-567: Mutant Huntingtin Impairs the Recruitment and Activation of Motor Proteins to BDNF-Endosomes

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Huntingtin (htt) scaffolds adaptors and motor proteins to vesicular cargoes. Htt-directed transport mediates transcription, nucleocytoplasmic shuttling, synaptic function, and apoptosis. Huntington's Disease (HD) is a polyQ disorder characterized by polyglutamine expansion of lengths >35Q at the N-terminus of HTT, with increasing repeat length corresponding to earlier onset of neurodegeneration. Cells expressing polyQhtt exhibit defects in transport of brain-derived neurotrophic factor (BDNF) and lysosomes. We aim to understand how polyQhtt perturbs the interactions between motor proteins, vesicular cargoes, and cytoskeletal components in the transport complex, and how defects in transport contribute to HD. We track BDNF-cargoes and degrative lysosomes in neurons induced from gene-edited, isogenic human stem cell lines with 18, 30, 45 and 81 polyQ repeats in HTT. We have developed methods to isolate cargoes, reconstitute and visualize their motility along microtubules in vitro, and quantify the motors and adaptors bound to them. Our preliminary results suggest that BDNF-containing cargos co-localize with lysosomes 60-90 minutes post-internalization. Frequent colocalization occurs earlier in normal htt than in polyQhtt conditions, suggesting mutant HTT may delay maturation of degradative cargoes. Additionally, isolated BDNF-cargoes from mutant HTT neurons exhibit more diffusive patterns in motility, indicating that polyglutamine expansions may impair transport.

P3-B-568: Patient-derived NMDA receptor mutation causes distinct synaptic and dendritic pathologies: Insights into treatments for GRIN1 epileptic encephalopathy

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Mutations in NMDA receptor (NMDAR) encoding GRIN genes are an emerging cause of epileptic encephalopathy, characterized by profound developmental delay and seizures. Patient specific GRIN mutations cause varying symptom severity and neural deficits, complicating a general understanding of GRIN disorders. While previous studies focus mainly on synaptic NMDARs in GRIN mutations, the impact on extrasynaptic NMDARs with integrative capacity and dynamic interactions with local ion channels remains enigmatic. To obtain a broad understanding of relevant neurophysiological changes, we study a mouse model carrying the Y647S patient mutation in GRIN1 encoding for the obligate GluN1 subunit. Electrophysiology experiments in brain slices from Grin1 Y647S+/- mice of both sexes reveal complex synaptic and dendritic mechanisms causing pathological hyperexcitability. Specifically, we identify a

dichotomy in deficits involving synaptic versus extrasynaptic NMDAR activation. Isolated synaptic NMDAR currents are significantly smaller in Y647S+/- mice, whereas extrasynaptic NMDAR-dependent dendritic plateau potentials are aberrantly prolonged. The pattern is consistent with failure of an extrasynaptic brake mechanism known to prevent epileptiform activity: NMDAR recruitment of Ca2+ activated SK potassium channels. Boosting SK channel activity restored appropriate timing to dendritic plateau potentials, reducing hyperexcitability. These findings highlight the importance of evaluating NMDAR function in intact neural circuits to determine treatment strategies for GRIN disorders.

P3-B-569: Muscarinic M3 receptor activation influences the excitability of layer VI pyramidal neurons of the medial prefrontal cortex

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The normal cholinergic response in pyramidal neurons of the medial prefrontal cortex (mPFC) has been described, within layers II/III and V, to be dependent solely on the muscarinic M1 receptor. In contrast, recent pharmacological findings from our group suggest that the cholinergic response in pyramidal neurons within layer VI depends on both the M1 and M3 receptor. This current study investigated the role of the M3 receptor on the cholinergic response in pyramidal neurons within layer VI of the mouse mPFC using pharmacological and genetic manipulations. All experiments employed whole-cell electrophysiological recordings to measure excitability responses to muscarine (30 µM) applied focally within brain slices. In naïve animals, pre-exposure to M3 receptor-selective antagonists at minimally effective concentrations (4-DAMP at 10 nM and 100 nM, and darifenacin at 1 µM) significantly decreased the cholinergic response in both sexes. Similar results were observed by knocking-down M3 receptor content genetically via bilateral injection of either an siRNA targeting the M3 receptor or a scramble siRNA negative control. In these ongoing experiments, preliminary findings show that the cholinergic response is significantly lower in knockdown animals compared with control animals in both sexes. Findings from this study confirm an important role of the M3 receptor to mediate normal cholinergic responses in mPFC layer VI neurons, which likely influences their contribution to prefrontal cognitive networks.

P3-B-570: NAV1.6 channels amplify spine potentials and are required for synaptic plasticity.

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Dendritic spines are the main receptacles of excitatory information in the brain. Their particular morphology, with a small head connected to the dendrite by a slender neck, has inspired theoretical and experimental work to understand how these structural features affect the processing, storage and integration of synaptic inputs in pyramidal neurons (PNs). The activation of glutamate receptors in spines triggers a large voltage change as well as calcium signals at the spine head. Thus, voltage-gated sodium (Nav) channels located in the spine head likely play a key role in synaptic transmission and plasticity.

Indeed, it has been shown that tetrodotoxin (TTX)-sensitive Nav channels boost synaptic potentials at the spine for tens of milliseconds after the onset of the response in layer 5 PNs (Araya et al., 2007 PNAS). These results suggest that a persistent sodium conductance is present in spines. To uncover the molecular identity and function of this spine Nav channel we used a combination of molecular, pharmacological, electrophysiological and optical tools. Our results show that the Nav1.6 channel isoform is localized in PN dendrites and spines, and its activity, characterized by a transient and persistent inward current, boost synaptic potentials and is required for the induction of spike-timing dependent plasticity (STDP). In accordance with our experimental data, numerical simulations predict that synaptic inputs impinging onto spines generate large voltage responses within the spine head itself, which are sufficient to activate Nav1.6 channels and boost spine potentials. These results show for the first time that Nav1.6 channels are activated in spines and required for the induction of STDP in cortical PNs.

P3-B-571: Interrogating the mechanistic role of ISR activation in microglial reactivity

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Microglia are the sentinels of the central nervous system, responsible for initiating the innate immune response when challenged by pathogens, trauma, or disease. The transient activation of microglia is key to maintaining tissue homeostasis and neuronal function. However, the intrinsic machinery contributing to acute microglial reactivity and subsequent resolution of their activated phenotype is poorly understood. The integrated stress response (ISR) is a cytoprotective signalling cascade attuned to various intracellular stressors, resulting in the transient upregulation of activating transcription factor 4 (ATF4). Acute ISR activation is key for the induction of homeostatic effectors, however, sustained activation is attributed to intracellular dysfunction. Given the putative role of the ISR in maintaining cellular homeostasis, it is an attractive target to interrogate as a modulator of microglia activation and resolution. Thus, we aim to characterize the mechanistic role of the ISR in mediating microglial reactivity in response to stressors akin to the cellular environment. We have demonstrated in vitro, primary microglial reactivity is concomitantly associated with the activation of the ISR, wherein conditional ATF4 loss of function ameliorates cytokine release. Further, inhibiting ISR function via small molecule inhibitors and shRNA knockdowns of PERK, PKR and eif2a under conditions of proteolytic and metabolic stress is protective. ISR inhibition significantly ameliorates both the phenotypic markers of microglial reactivity and pro-inflammatory cytokines; this enhances microglial survival and homeostatic morphology. Taken together, we have demonstrated a novel mechanism of microglial activation, implicating the ISR as a key mediator of microglial reactivity.

P3-B-572: In Vivo Neuronal Imaging to Quantify SYNGAP1 Missense Mutations Effects on Plasticity

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Autism Spectrum Disorder (ASD) is the most common genetic neurodevelopmental disorder, and yet it has no effective treatment. As a spectrum disorder, individuals with ASD present with a wide range of impact on cognitive ability, communication, and social interactions. Although large exome sequencing studies implicate hundreds of genes in ASD, a handful of genes are tightly linked, including Synaptic Ras GTPase-Activating Protein 1 (SYNGAP1). SYNGAP1 is an intriguing ASD candidate gene since it functions as a master regulator of plasticity, deciding whether neuronal synapses are strengthened (long-term potentiation (LTP)) or weakened (long-term depression (LTD)). Previously, we have tested the biochemical impacts of 23 ASD associated missense variants of SYNGAP1 and found that the mutated protein function is not lost, instead the mutations selectively impacted either LTP or LTD molecular cascades. Here we perform population activity and single neuron structural measures of in vivo developing neurons that are exogenously expressing SYNGAP1 missense mutations. These metrics are used to indicate whether a specific SYNGAP1 missense mutation influences a neuron to undergo LTP or LTD. This approach to investigating specific disease associated missense mutations will give insights into the spectrum nature of ASD and lead to development of targeted and precise therapeutics based on the exact mutation that a person with ASD has.

P3-B-573: Investigating the effects of increasing the cortical excitability of the primary motor and dorsolateral prefrontal cortices in trained runners

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Background: The primary motor cortex (M1) is a brain region that sends outputs to initiate voluntary contraction, while the dorsolateral prefrontal cortex (DLPFC) is involved in cognitive processes such as motivation. There is evidence of a functional connection between these regions. Repetitive Transcranial Magnetic Stimulation (rTMS) can alter the cortical excitability of these two regions, which may further our understanding of the connection between DLPFC and M1. To our knowledge, the effect of rTMS applied to both M1 and DLPFC has not been studied. Methods: Ten trained runners (six males, aged 20-42 years old) took part in four experimental visits. One of the 4 possible combinations of either excitatory rTMS or sham rTMS was applied to M1 and the left DLPFC at each visit. After rTMS, the athletes performed a 3-km run. Motor Evoked Potentials (MEPs) obtained by stimulating the M1 representation of the bilateral tibialis anterior muscles (TA) quantified M1 excitability. We analyzed MEPs using Friedmans' Two-Way Analysis of Variance by Ranks. We obtained MEPs at timepoints pre rTMS (T1), immediately post-rTMS (T2) and after the 3-km run (T3). Results: There was a significant decrease in mean peak-to-peak MEP amplitude in the right TA from T1-T3 in the rTMS DLPFC M1 condition ($p = 0.02$). Conclusion: MEP amplitude in the right TA decreased after rTMS was applied to both DLPFC and M1. This may be due to an inhibitory drive from DLPFC to M1. Only seen in the right TA, this effect could also stem from an intrahemispheric inhibition as rTMS was applied to the left DLPFC.

P3-B-574: The wiring and synapse specificity of cerebellar mossy fibers to inhibitory targets is regulated by atypical cadherins.

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A critical step in brain circuit formation is the precise assembly of excitatory and inhibitory connections. The cerebellum receives complex cortical information primarily via mossy fiber (MF) projections from brainstem structures to the cerebellar granule layer. These MF projections connect excitatory cerebellar granule cells (GC) and inhibitory Golgi cells (GoC) from the same presynaptic terminal. Adhesion molecules involved in the formation of MF-GC synapses have been identified but factors that promote the formation of MF-GoC synapses are unknown. We recently identified the adhesion molecule, Cadherin-23 (Cdh23), in cerebellar inhibitory interneurons. Since Cdh23 mRNA is selectively expressed in both GoC and MF afferents, we propose that Cdh23 mediates synaptic targeting and specificity between MF and GoCs. In support of this hypothesis, our mis-expression studies in vivo and in vitro and analyses of Cdh23 knockout mice indicate roles for Cdh23 in promoting MF-GoC connectivity. I will present my characterizations of conditional Cdh23 mouse mutants to determine whether cellular and synaptic connectivity defects result from pre- or post-synaptic loss of Cdh23. I will present ongoing work on the role of Cdh23 in regulating synapse specificity through homophilic interactions or with its canonical binding partner. Together, these studies are the first to investigate synapse formation on cerebellar GoC and the specificity of targeting inhibitory versus excitatory cells.

P3-B-575: The transcription factor Zfh2 acts in glia to regulate CNS development and motor behavior.

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Glial cells play critical roles in shaping the development and function of the central nervous system (CNS). However, much remains to be learned about how different glial cell types interact with neurons to regulate their physiology. The Drosophila CNS contains three glial cell types that are intimately associated with neurons - astrocytes, ensheathing glia and cortex glia. From single-cell RNA sequencing data we made an inventory of genes specifically enriched in these distinct glial cell types for which we performed RNAi-based loss-of-function screening. We identified 6 factors causing motor deficits when knocked down selectively in either astrocytes, ensheathing glia or cortex glia. Interestingly, the highly conserved transcription factor Zn finger homeodomain 2 (Zfh2) was required in glia for proper motor behavior and glial morphology. Zfh2 showed a dynamic expression pattern in the CNS during larval and adult development. Knockdown of Zfh2 in specific glial cell types led to larval crawling deficits, decreased adult climbing ability or adult paralysis behaviors. Loss of Zfh2 from distinct glial cell types led to morphological deficits suggesting that Zfh2 may be required for proper glial differentiation. Ongoing research to clarify the mechanisms by which Zfh2 regulates glial cell development and CNS function will be presented.

P3-B-576: ALTERED INTEGRATION OF EXCITATORY INPUTS ONTO THE BASAL DENDRITES OF LAYER 5 PYRAMIDAL NEURONS IN A MOUSE MODEL OF PHELAN-MCDERMID SYNDROME

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Phelan-McDermid syndrome (PMDS) is a rare multisystemic disorder with a high prevalence of autism spectrum disorders. Diagnostic criteria for PMDS include mutation or deletion of the gene SHANK3. SHANK3 encodes a scaffolding protein, enriched in the postsynaptic density of excitatory synapses where it interacts with other proteins to promote dendritic spine development and maturation. Excitatory inputs onto cortical layer 5 pyramidal neurons (L5PNs) arrive at dendritic spines where they are processed, stored, and integrated by dendrites. In vitro studies in the cortex of Shank3-deficient mice have shown defects in synaptic transmission and plasticity, an impairment in spine density and morphology as well as channelopathies. However, it remains unknown how excitatory inputs are processed and integrated in the dendrites of Shank3-deficient L5PNs. To uncover how synaptic integration of sensory inputs in the basal dendrites of L5PNs is affected in PMDS, we performed two-photon uncaging of caged glutamate to activate single and multiple spines while recording their somatic voltage responses in mice heterozygous for a Shank3 deletion (Shank3 /-), a well-established mouse model of PMDS. Our results show that while subthreshold excitatory inputs integrate linearly in wild-type L5PNs, they summate supralinearly in those from Shank3 +/- mice. These results suggest sensory inputs are over-represented in basal dendrites of L5PNs from a PMDS mouse model, which could explain at least in part the sensory hypersensitivity usually observed in autism spectrum disorders.

P3-B-577: Semaphorin 3a is an evolutionarily conserved signal for the rapid homeostatic modulation of excitatory synaptic transmission in the adult mouse hippocampus

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Presynaptic homeostatic plasticity (PHP) rapidly controls presynaptic neurotransmitter release to offset pharmacological and genetic impairments in postsynaptic neurotransmitter receptor function. We have recently shown that PHP can be induced within minutes at adult mouse hippocampal synapses, requires postsynaptic NMDAR function, and involves the coordinated growth of pre- and postsynaptic elements, as determined by ultrastructural reconstruction of hippocampal volumes. Currently, the signaling effectors controlling PHP in the adult mouse brain remain completely unknown. At the Drosophila NMJ, the secreted semaphorin 2b is a retrograde signal essential for the expression of PHP. Here, we demonstrate that hippocampal PHP requires semaphorin 3A (Sema3A), a mouse homologue of Drosophila sema2b. Sema3A is strongly expressed in the CA1 pyramidal neuron layer and neuron-specific loss of Sema3A completely impairs the expression of PHP. Mice harboring loss-of-function point mutations that selectively impair Sema3A-to-neuropilin1 signaling (Sema3AK108N mice) also lack PHP in a gene-dosage dependent manner. Preliminary ultrastructural evidence suggests that active zone growth associated with PHP is lost in Sema3AK108N mice. Finally, we demonstrate that soluble wild-type

Sema3A protein rescues PHP in Sema3AK108N mutant mice via modulation of the readily releasable pool of synaptic vesicles. Together, our findings suggest that the secreted semaphorins represent an evolutionarily conserved signaling feature of PHP in the adult mammalian brain.

P3-B-578: Radial astrocytes in the developing retinotectal system are activated by norepinephrine and promote visually-driven escape behaviour

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The retinotectal system of Xenopus laevis is populated by radial astrocytes, a cell type which functions as both neural progenitor and partner in synaptic development and function. An understanding of how glial cells, such as radial astrocytes, actively influence neural circuit function during early development of sensory systems has remained largely elusive in vivo. By systematically using visual stimulation along with pharmacological manipulation and chemogenetic activation of cells in the tectum of Xenopus tadpoles expressing GCaMP6s, we are beginning to understand how radial astrocytes integrate and influence sensory-evoked neuronal activity in ways that also influence behaviour. Here we show that the activation of tectal radial astrocytes induces a state switch in the tectum which biases the system towards the detection of threatening visual looming stimuli by suppressing the detection of non-loom related visual information. We show that his effect involves the activation of alpha1 adrenergic receptors by norepinephrine, the involvement of gap junctions/hemichannels, and the probable release of ATP/adenosine. Complementary electrophysiological recordings from postsynaptic tectal neurons suggest that norepinephrine reduces presynaptic input in the tectum. Additionally, we show that the targeted chemogenetic activation of tectal radial astrocytes in freely swimming animals nearly doubles loom-evoked escape rates suggesting that radial astrocytes may play an important role in mediating the probability of initiating escape behaviour during predation events.

P3-B-579: Investigating a role for netrin-1 in long-term potentiation

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Long-term potentiation (LTP) is an activity dependent form of plasticity that strengthens glutamatergic synapses and serves as a cellular model of learning and memory formation. We have demonstrated that netrin-1, a secreted chemotropic cue that regulates cell migration, axon guidance and synaptogenesis during neural development, is required and sufficient for the initial phases of LTP by rapidly recruiting GluA1 containing AMPA receptors to Schaffer collateral synapses in adult mouse. Independent findings indicate that netrin-1 can rapidly initiate protein synthesis through local translation in neurons. LTP exhibits a specific protein synthesis dependent late phase, suggesting that these long-term protein synthesis dependent changes in synapse strength might be regulated by netrin-1. Here, we provide evidence that brief bath application of netrin-1 results in a persistent potentiation of Schaffer collateral synaptic responses that lasts for greater than 4 hours in adult hippocampal brain slices, indicating that netrin-1 induced synaptic strengthening is long-lasting. Our ongoing studies utilizing genetically modified

mice and electrophysiological analyses aim to determine if the late phase of netrin-1 induced synaptic potentiation requires protein synthesis, and if neuronal expression of netrin-1 is required for the late protein synthesis dependent phase of LTP.

P3-B-580: Targeting palmitoylation of p62 as a therapeutic approach towards Huntington Disease

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Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder that is caused by a mutation in the huntingtin gene that results in the accumulation of mutant HTT protein (mHTT) and disruption of many cellular pathways causing neuronal cell death. Lowering mHTT levels has become a primary therapeutic strategy for HD. Autophagy, an intracellular clearance pathway is disrupted in HD. mHTT aggregation in HD is believed to stem from the cargo-loading defect during autophagy resulting in empty autophagosomes. p62 is an autophagy receptor responsible for delivering misfolded proteins and aggregates to autophagosomes and eventually lysosomes for degradation. We have identified that p62 is palmitoylated. Palmitoylation is a critical post-translational modification required for protein trafficking and membrane associations. The dynamic nature of palmitoylation may allow for the re-localization of toxic proteins to the autophagosomes. Palmitoylation of p62 is significantly reduced in the cortex of HD patients and the YAC128 HD mouse models. We predict that rescuing p62 palmitoylation will improve cargo loading and promote the clearance of toxic aggregates. A high-throughput screen of FDA-approved drugs previously identified a candidate that could penetrate the blood-brain barrier and may increase palmitoylation. I have confirmed that p62 palmitoylation indeed increases in response to the identified drug with a concomitant increase in localization to autophagosomes in HeLa cells. The investigations thus far suggest that this drug is capable of rescuing palmitoylation of p62 and may be a novel depalmitoylation inhibitor. Therefore, understanding the underlying mechanism of this drug will be integral in identifying new therapeutic targets for HD.

P3-B-581: Diversity in the activation profiles of primate cortical pyramidal neurons induced by electrical stimulation measured by two photon Ca++ imaging

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A hierarchy of intrinsic timescales of neuronal activation across the different sensory and association cortical areas is a potential mechanism by which cortex encodes and maintains information in working memory for longer periods of time (Murray et al., Nat. Neurosci. (2014), 17 (12), 1661-1663). The timescales of activation of neurons as measured by their autocorrelation function during cognitive tasks shows a gradient along the cortical hierarchy from sensory to prefrontal association areas. Several mechanisms could contribute to the longer timescales in the neuronal autocorrelation functions in association cortices. Ca++ imaging with genetically encoded indicators such as GCaMP in cortical slices combined with electrical microstimulation offers an attractive methodology to examine the response

profiles of many neurons simultaneously to further address the mechanisms by which activation timescales vary between different areas. Here we performed two photon microscopy while electrically stimulating cortical slices from the common marmoset, Callithrix jacchus. We virally expressed GCaMP6f in diverse marmoset and murine cortical areas under the control of the CAMKII promoter. We characterized the time-course, latency of onset, amplitude, and other parameters of Ca++ responses of pyramidal neurons to electrical stimulation of prefrontal and sensory cortical slices with and without blockade of ongoing synaptic transmission. Additionally, we examined spontaneous Ca++ oscillations in cortical slices in a modified ACSF that is previously shown to induce slow oscillations in ex vivo preparations. We show that there is considerable diversity in the stimulation-induced and spontaneous Ca++ activation dynamics of cortical pyramidal neurons.

P3-B-582: Pannexin-1 regulates dendrite branching and dendritic spines formation in hippocampal neurons by modulating actin polymerization through Rac1/RhoA small-GTPase

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Small Rho GTPases, RhoA, Rac1, and Cdc42, play an essential role in regulating structural plasticity by controlling the assembly and stability of the actin cytoskeleton; little is known about the signals that activate or inhibit small Rho GTPases. Pannexin 1 (Panx1) channels are implicated in actin-dependent processes, such as neurite extension and spine formation. Given this, we ask whether Panx1 channels modulate actin remodeling-dependent structural plasticity in hippocampal neurons through a mechanism that involves Rho GTPases. To address this, we treated cultured mouse hippocampal neurons with Panx1 blockers or Rac1/RhoA inhibitors. We then induced long-term potentiation with glycine (gly-LTP), measured: neuronal morphologies and F-actin content, and quantified activated Rac1/ RhoA. Blocking Panx1 induced greater dendritic complexity and higher spine density following gly-LTP, increased F-actin content, and modified the activated form of Rac1/RhoA. Rac1 inactivation prevents the effect of Panx1 inhibition on dendritic arborization and spine density. Finally, RhoA inhibition did not affect morphology. Our findings suggest that Panx1 with Rho GTPase signaling plays a role in regulating neuronal morphology by modulation of F-actin content through Rac1/RhoA GTPase activity. Thus, the functional interaction between Panx1 channels and Rho GTPases could be of pivotal relevance to contributing to new strategies to treat neurodevelopmental disorders, which are manifested with abnormalities in the neuronal actin cytoskeleton.

P3-B-583: The role of astrocytes on clock neurons circadian plasticity

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A group of D. melanogaster key circadian neurons, the small lateral ventral neurons (sLNvs), undergoes daily changes in their dorsal termini. This phenomenon, called circadian structural plasticity, correlates with the modification of active zones and synaptic partners. These rhythmic changes, aside from

depending on diverse neuronal properties, rely on a functional clock in glial cells. Here, we study how the glia-neuron communication affects the remodeling of the sLNvs. First, using GFP reconstitution assays (that relies on GFP expression of two complementary non-fluorescent GFP fragments in neurons and glial cells; only those that are in close proximity will result in a fluorescent contact), we found that sLNvs termini directly contact two different glial subtypes (astrocyte-like and ensheathing glia) and that these contacts are time-of-the-day dependent. Next, we found that blocking adult gliotransmission (i.e., in the astrocytes) dampens structural remodelling without affecting PDF neuropeptide levels; and that knocking down maverick (a ligand of the BMP pathway, a potential gliotransmitter candidate) in the astrocytes has a similar effect . Taken together, our results suggest that astrocytes play an important role on sLNvs structural plasticity by releasing specific factors such as maverick and, in turn, changing the degree of connectivity (hence, support) with neurons along the day.

P3-B-584: RyR-mediated Ca2+ release elicited by neuronal activity induces nuclear Ca2+ signals, CREB phosphorylation, and Npas4/RyR2 expression

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Introduction: The expression of hippocampal genes involved in synaptic plasticity requires that neuronal activity-induced Ca2+ signals reach the nucleus. Through Ca2+-induced Ca2+-release, the endoplasmic reticulum-resident ryanodine receptor (RyR) Ca2+ channels amplify and propagate Ca2+ entry signals in neurons. The rodent hippocampus expresses mainly the RyR2 isoform, with lower expression levels of RyR3 but almost undetectable levels of RyR1. Here, we tested whether RyR2/3 channels contribute to nuclear Ca2+ signal generation. Methods: We used GCaMP3.NLS to study nuclear Ca2+ transients in rat primary hippocampal cultures treated with gabazine (GBZ) to increase neuronal activity. Ryanodine was used to suppress overall RyR activity and a shRyR2 construct to knockdown RyR2 expression. We measured CREB phosphorylation and RyR2/3 distribution by immunostaining, while Npas4/RyR2 gene expression was measured by RT-qPCR. Results: Neuronal soma and neurites expressed both RyR2/3 channel isoforms, while dendritic spines expressed only RyR3. Ryanodine treatment and shRyR2 significantly reduced GBZ-induced nuclear Ca2+ signals. Ryanodine treatment also prevented the GBZ-induced CREB phosphorylation and enhanced Npas4/RyR2 expression. Discussion: We conclude that RyR-mediated Ca2+ release contributes to the sequential generation of nuclear Ca2+ signals, CREB phosphorylation, Npas4, and RyR2 up-regulation. We propose that the RyR3 isoform amplifies activity-generated Ca2+ entry signals at the dendritic spines, which reach the dendrites and activate primarily RyR2-mediated Ca2+ release.

P3-B-585: Understanding dynamic palmitoylation of Shaker-related voltage-gated potassium ion channels (Kv1) at the axon initial segment

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The axon initial segment (AIS) is a specialized compartment residing between axonal and somatodendritic domains that is the site of action potential initiation within neurons. There is a high density of various voltage-gated ion channels, including sodium (Nav1) and potassium (Kv1) channels, at the AIS, which are critical for initiating and shaping action potentials, respectively. The disruption in Kv1 trafficking is associated with various channelopathies including episodic ataxia type-I and epilepsy, emphasizing the importance of Kv1 channels in neuronal function. Still, the mechanisms governing the precise AIS distribution of Kv1 channels remain poorly understood. The AIS is dynamic and plastic, such that there are alterations in morphology and ion channel composition in response to neuronal activity. The post translational lipid modification, palmitoylation is critical for the clustering of Kv1 channels at the AIS. Palmitoylation involves the covalent attachment of long-chain fatty acids to cysteine residues via a thioester linkage. Importantly, the reversible nature of palmitoylation makes it well suited to dynamically regulate Kv1 channel localization in response to changes in neuronal activity. My preliminary data, strongly suggests that Kv1 channels undergo cycles of palmitoylation and depalmitoylation but also give insight as to the Kv1 channel depalmitoylating enzyme. The results of this research may offer a greater understanding of the mechanisms involved in dynamic Kv1 AIS targeting and could offer novel therapeutic targets for treating various Kv1 related channelopathies.

P3-B-586: Sex-dependent effects of homozygous Mapt deletion on synaptic plasticity in adult rats

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Dysfunction of the tau protein defines tauopathies, a group of sex-dependent neurodegenerative disorders (PMID: 8832649). To understand physiological functions of tau, we created a novel CRISPR-Cas9 microtubule-associated protein tau homozygous knock-out (Mapt-/-) rat model which exhibits sex-dependent synaptic plasticity phenotypes at post-natal day (P) 14-18 (Ralph et al., 2022, FENS). Briefly, in comparison to littermate-matched wild-type controls, P14-18 Mapt-/- female rats showed increased long-term potentiation (LTP) whereas Mapt-/- male rats displayed increased long-term depression (LTD) at Schaffer collateral/commissural (SC)-CA1 synapses. Considering that tauopathies manifest in adulthood and synaptic plasticity is regulated by puberty and other age-related effects, we wanted to next determine whether these sex-dependent effects on synaptic plasticity are evident in Mapt-/- rats at 1 year of age. In a blinded manner, we performed electrophysiological recordings of SC-CA1 synapses in transverse hippocampal slices. We found that as in P14-18 Mapt-/- rats, female Mapt-/- rats displayed increased LTP, and male Mapt-/- rats exhibit increased LTD. Also, consistent with our previous study of P14-18 rats, basal synaptic transmission, and probability-of-neurotransmitter release are unchanged in both sexes of Mapt-/- rats. Collectively, our results suggest the tau protein regulates long-term synaptic plasticity in a sex-dependent fashion across the lifespan of rats.

P3-B-588: The role of orexin type-1 receptors in the development of morphine tolerance in locus coeruleus neurons

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Objective: Long-term exposure to opioid agonists results in tolerance to their analgesic effects, so the effectiveness of opioid agonists in the management of pain becomes limited. The locus coeruleus (LC) nucleus has been involved in the development of tolerance to opiates. Orexin type-1 receptors (OX1Rs) are highly expressed in LC nucleus. Orexin plays a noteworthy role in the occurrence of morphine tolerance. The purpose of the present study is to investigate the role of orexin type-1 receptors in the development of morphine tolerance in LC neurons. Method: In this study, adult male Wistar rats weighing 250-300g were utilized. Induction of morphine tolerance was obtained by single injection of morphine per day for 6 successive days. An orexin type-1 receptor antagonist (SB-334867) was injected into the lateral ventricle instantly prior to morphine injection. On day 7, the effect of morphine on the electrical activity of LC neurons was studied using in vivo extracellular single unit recording. Results: The results demonstrate that morphine injection for 6 consecutive days led to the development of morphine-induced tolerance in LC neurons. In other words, there was a significant decrease in LC neuronal responsiveness to morphine injection. Inhibitory responses of LC neurons to intraperitoneally applied morphine can be observed with the treatment of the SB-334867 prior to morphine injection. Conclusion: This study showed that OX1R blockade by SB-334867 prevents the development of morphine tolerance in LC neurons.

P3-B-589: Ketogenic diet promotes social stress resistance and modifies microglial morphology and ultrastructure in male mice

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Ketogenic diet (KD) is high-fat, low-carbohydrate diet which may promote stress resilience. Microglia are the resident immune cells of the brain; they coordinate brain immune responses and can react to psychological stress and mediate stress-related brain changes. This study focused on the effect of KD, its relationship to stress resilience and its effect on microglia. Two-month-old adult male C57BL/6 mice received KD versus control diet (CD) starting 4 weeks prior to the experiment. The dietary effects on the response to chronic stress were investigated by comparing non-stressed controls with animals undergoing 10 days of repeated social defeat (RSD). After RSD, mice were classified as resilient or susceptible to stress based on a social interaction test. KD increased the proportion of resilient mice compared to CD. We studied the underlying mechanisms by focusing on microglia in the ventral hippocampus, a region affected by chronic stress. Using TMEM119/IBA1 double staining, we found that KD does not affect microglial number or distribution. However, changes in their soma and arborization area were linked to the effect of diet and stress. Ultrastructural analysis of microglia by electron microscopy showed that KD reduced the number of markers of cellular stress. Microglia also displayed general effects of stress in the number of contacts with synaptic elements. Lipidomic analysis of hippocampus showed distinct lipidomic signatures. This study provides valuable results regarding the dynamic relationship of diet-induced energetic shifts, psychological stress, and microglia.

P3-B-590: Role of AMPA glutamate receptors in hippocampal synaptic plasticity and neuronal activation during learning and memory

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It is believed that memories are physically represented within specialized structures between neurons known as synapses. Under certain conditions, synaptic strength can be robustly increased or decreased to produce long-term potentiation (LTP) or depression (LTD), and these processes involve alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs). Learning also induces the activation of selected neurons (known as engram cells), however a mechanistic link between synaptic plasticity and learning-induced cell activation remains unknown. This study uses male and female adult age-matched C57BL/6J wildtype and transgenic mice featuring genetically modified AMPARs and impaired LTP and LTD to investigate the role of AMPAR-mediated changes in synaptic plasticity on learning-induced cell activation. It was hypothesized that AMPARs are modified specifically in learning-induced active cells and that deficits in synaptic plasticity will impair engram cell activation. Mice injected with a robust activity-dependent viral marker into the hippocampus, a critical memory structure, underwent contextual fear conditioning to form a long-term context-dependent memory. We report that transgenic mice deficient in long-term contextual fear memory and synaptic plasticity featured a reduction in learning-induced active cells in the hippocampal dorsal CA1 region relative to wildtype littermates. Follow-up studies are underway to examine potential morphological changes in dendritic spines as well as associated functional impairments using ex vivo whole-cell recordings.

P3-B-591: Opioids differentially regulate transmission from subclasses of prefrontal GABAergic interneurons

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Opioid signaling is strongly associated with motivation and reward, and as such has a high liability for abuse and addiction. Opioid receptors are expressed throughout limbic and cortical structures, including in GABAergic interneurons, but the cellular mechanisms by which opioids regulate circuit function are unclear. Here we demonstrate that delta opioid receptors (DORs) differentially modulate GABAergic inputs in prefrontal cortex (PFC). Application of the DOR-selective agonist DPDPE strongly suppressed electrically-evoked inhibitory currents on layer 5 pyramidal neurons, but had variable effects on short-term plasticity (STP). Optogenetic targeting of select GABAergic subpopulations in PFC revealed that DPDPE suppressed transmitter release from both parvalbumin- (PV+) and somatostatin-expressing (SOM+) interneurons, but with notable differences. PV+ neurons exhibit canonical presynaptic depression accompanied by a significant STP increase, while in SOM+ terminals GABA release is suppressed without corresponding STP changes. Surprisingly, single bouton calcium imaging demonstrated that DPDPE reduced action potential-evoked transients in both subtypes, and we are currently investigating the possibility of differential calcium channel regulation. These results demonstrate that the same opioid receptor can regulate inhibitory synapses via multiple mechanisms,

even within the same cortical microcircuit. Since inhibitory neurons gate the flow of information through PFC circuitry, subtype-specific release modulation has significant implications for opioid research.

P3-B-593: Astrocyte glucocorticoid signaling mediates cognitive impairment induced by early-life stress

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Early-life stress can have lifelong consequences, enhancing stress susceptibility and resulting in behavioural and cognitive deficits. While the effects of early-life stress (ELS) on neuronal function have been well-described, we still know very little about the contribution of non-neuronal brain cells to the cellular and behavioural adaptations following ELS. Here, using a rodent model of ELS, we report that astrocytes play a key role in mediating the impact of stress on amygdala-dependent behaviour and synaptic plasticity during adolescence. We report that ELS induces generalisation of fear, associated with increased levels of circulating corticosterone and activation of glucocorticoid receptors in astrocytes. In addition, we identify astrocyte glucocorticoid receptors as targets, mediating ELS-induced cognitive and synaptic impairments. This work establishes astrocytes as key elements in amygdala-dependent memory, and as central mediators of the effects of stress on cognitive function via stress hormone signalling pathways.

P3-B-594: 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 an excessive number of synapses during early brain development, called synaptogenesis. To establish a mature and functional network, our brains need to eliminate the excess synapses according to their signal strength. Microglia, the brain residue macrophages, participate in both synaptogenesis and synaptic pruning. Aberrant microglial clearance of synapses can cause serve 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 constructed a human induced pluripotent stem cell (iPSC)-based co-culture system containing both neural cells and microglia. To investigate how microglia regulate neural network development, I combined traditional molecular and immunostaining assays with the Multi-Electrode Array (MEA) technology to characterize the synaptogenesis and synaptic elimination in the co-cultures. I also challenged the co-culture with interferon γ (IFNγ) and the TLR4 ligand lipopolysaccharide (LPS) to drive the pro-inflammatory phenotype of microglia. Our preliminary results showed that IFNγ/LPS stimulation can increase the microglial engulfment of presynaptic compartments.

Finally, to investigate the molecular mechanism regulating synaptic elimination, I constructed the complement component C1QA knockout cell lines and differentiated C1QA knockout microglia to build the co-cultures. My co-culture system will significantly extend the toolbox to study the human-specific features during brain development and pathology.

P3-B-595: Brain pericytes are highly vulnerable to oxidative stress

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Brain dysfunction in disorders such as stroke, Parkinson's, and Alzheimer's disease is mediated, in part, by oxidative stress (OS) - a pathological state caused by an excess of reactive oxygen or nitrogen species. These molecules impede brain function by oxidizing proteins which control fundamental cellular functions and can cause cell death. As such, it is vital to identify the central cellular and molecular targets modified by OS underlying brain dysfunction. We pursued this using two-photon microscopy to examine cell death during OS in rodent cortical brain tissue. Using propidium iodide (PI) uptake as a death assay, we found that 10-min exposure to a thiol oxidizing agent was sufficient to elicit cell death. Interestingly, the rapidly dying cells were associated with the vasculature. Based on their discrete morphology and association with the basal lamina, we examined whether the vulnerable cells were pericytes. Live imaging of pericytes labelled with the fluorescent marker NeuroTrace (NT), revealed that tissue oxidation produced simultaneous PI uptake and NT loss in a large fraction of pericytes within minutes. By contrast, there was significantly less PI uptake by non-pericyte cells. Our results demonstrate that pericytes are highly sensitive to pathological changes in redox state. Pericytes have important roles in regulating blood vessel stability, blood brain barrier integrity, and cerebral blood flow. As such, our data indicates that pericyte dysfunction could be a central contributor to brain pathologies associated with OS. Future studies examining the mechanisms of heightened sensitivity of these cells to cell death during OS will be critical to test this hypothesis.

P3-C-597: The impact of early postnatal environment on the Cntnap2-knockout rat model for autism spectrum disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental condition affecting one in 160 children worldwide. The Cntnap2-knockout rat is a preclinical genetic model for studying ASD-related phenotypes. Previous work has demonstrated that homozygous Cntnap2-knockout (Cntnap2-/-) rats exhibit differences in communication patterns when bred and reared by a Cntnap2-/- compared to a heterozygous Cntnap2-knockout (Cntnap2+/-) dam. Building from this, the present research investigated if differences in postnatal environmental conditions imposed by breeding with a Cntnap2+/- or Cntnap2-/- dam also affect other ASD-related phenotypes in the Cntnap2-/- rat including auditory processing,

sensorimotor gating, and social behaviour. We implemented a cross-fostering paradigm in which Cntnap2-/- offspring were bred from a Cntnap2-/- dam but transferred to be reared by a Cntnap2+/- dam. We found subtle differences due to parental genotype and rearing conditions in measures of the auditory brainstem response, the startle response, and prepulse inhibition. Notably, although cross-fostering did not appear to affect juvenile play alterations observed in the Cntnap2-/- rats, it did restore social memory as assessed by a three-chamber social behaviour test. This research provides evidence that certain ASD characteristics observed in the Cntnap2-/- are not fixed by genetic predisposition but can be malleable by environmental conditions. Furthermore, the results have implications for how all researchers conduct breeding when using genetic animal models to study neurodevelopmental conditions.

P3-C-598: Effects of selective estrogen receptor activation on grooming behaviour in the Hole-Board Test following global-cerebral ischemia in female rats

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Estrogens have been shown to attenuate the neuronal death that results from global cerebral ischemia (GCI), which mimics cardiac arrest. However, conflicting literature shows estrogens to have anxiogenic or anxiolytic effects following GCI, highlighting a need for inquiry into estrogenic modulation of post-ischemic anxiety. Rodent models examining the effect of estradiol (E2) on anxiety-like behaviour suggest differential contributions of estrogen receptor (ER) subtypes, but very few studies have compared the contributions of ER subtypes in GCI models. The goal of this study is to investigate the effects of selective ER activation on anxiety-like behaviour following GCI. Female Wistar rats having undergone ovariectomy were divided into experimental groups receiving daily subcutaneous injections of propylpyrazole triol (PPT; ERα agonist), diarylpropionitrile (DPN; ERβ agonist), G-1 (G-protein coupled ER agonist; GPER), 17β-Estradiol (E2; to activate all receptors), or vehicle solution for 21 days. Rats were then subjected to GCI, using the 4-vessel occlusion (4VO) method or a sham surgery (having received vehicle injections). Anxiety-like behaviour was analysed in the Hole-Board Test. A one-way ANOVA found increased time spent grooming in the sham group compared to ischemic rats treated with PPT, E2, or vehicle. Interestingly, G-1 treated rats spent more time grooming than E2 rats. These results suggest that the anxiolytic effects of estrogens could be ERβ and GPER mediated. Further, these findings offer new insight into GPER's actions when activated alongside classical ERs.

P3-C-599: Identification of novel biomarkers on transcriptome profile of Parkinson's disease patients

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Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1-2% of the population over 65 years of age. PD is characterized by a preferential and massive loss of dopaminergic neurons (DN) in the substantia nigra. Even though the exact causes of DN loss in the substantia nigra of

PD patients are unclear, several lines of evidence support the involvement of autoimmune mechanisms in the etiology of PD. Our central hypothesis is that PD can impact the inflammatory/immune response of patients, which in turn can be reflected as a change in their transcriptomic and proteomic expression profile. Our goals are to i) characterize cellular models (Thp1 cells) where MitAP is either activated or repressed (PINK1-knockout or SNX9-knockout), ii) determine the immune profile of antigen presenting cells from PD patients and iii) assess if an inflammatory/immune signature is present in blood or serum of PD patients. This project will have a significant impact as it will increase our knowledge on the impact of MitAP in the immune response and define if these signatures are also observed in APCs of PD and atypical PD patients. In addition, it will define the global immune profile using a multi-omic approach in PD and atypical PD patients with the goal to determine omic signatures that could serve as biomarkers for early diagnosis.

P3-C-600: Investigation of novel ITPR1 variants in patients with late-onset ataxia

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Identifying the genetic causes of many diseases constitutes a major challenge for the scientific community. This is particularly true for diseases with high etiological and phenotypic heterogeneity, such as ataxias, neurological conditions affecting the cerebellum and impacting motor coordination. Our hypothesis is that combining molecular genetics with functional genomics will enable us to better understand the mechanisms underlying ataxic phenotypes in patients for whom traditional analyses have not resulted in a molecular diagnosis. Indeed, there are limitations inherent to standard testing practices for more complex cases (rare and highly heterogenous diseases, atypical presentations, etc.), such as the difficulty of interpreting variants of uncertain significance. We are currently investigating three novel variants of the ITPR1 gene discovered in patients with ataxia symptoms. In the absence of evidence supporting a deleterious impact of these variants, functional validation is necessary. This will involve determining their impact on the transcriptomic (qRT-PCR, long-read sequencing) and proteic (Western Blot) expression, and on the calcium release function of the ITPR1 receptor, via cellular models modified by Crispr-Cas9. Understanding the genetic causes of these rare diseases is essential to uncover their molecular mechanisms, and could ultimately lead to therapeutic strategies.

P3-C-601: EPRS1-related leukodystrophy: A genotype-phenotype correlation study reveals distinct neurological disease types and wide phenotypic variability

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Aminoacyl tRNA synthetases (ARS) are a group of ubiquitously expressed enzymes essential for catalyzing the esterification reaction to load amino acids onto their cognate tRNAs. A growing number of neurological disorders have been associated with mutations in ARSs. Glutamyl-prolyl-tRNA synthetase, EPRS1, is a bifunctional ARS with two catalytic domains joined by a linker region. Biallelic pathogenic variants in EPRS1 have been shown to cause an ultra-rare hypomyelinating leukodystrophy previously reported in 4 patients. Here, we present a cohort of 24 individuals from 20 families (19 previously unpublished patients) and expand the disease spectrum of EPRS1-related disorder. 26 new DNA sequence changes were detected, including 3 affecting splicing and 1 deletion. 10 individuals were found to display a novel disease phenotype. These patients do not have hypomyelination and display a milder clinical presentation characterized by developmental delay with or without ocular abnormalities, microcephaly and ataxia. In our cohort, neurological manifestations are universal, and visual loss (59.1%), short stature (31.8%), dental anomalies (31.8%) and sensorineural hearing loss (18.2%) were also commonly seen. Genotype-phenotype correlations revealed segregation of phenotypes to distinct protein domains, with most patients' mutations with hypomyelination clustering in the proline catalytic domain and of the mildly affected individuals' mutations concentrating within the glutamate catalytic core or the non-canonical appended domains. This study delineates the phenotypic landscape of EPRS1-related-disorder, broadening the disease spectrum.

P3-C-602: TDP-43 SUMOylation: A stress responsive modification linked to neurodegeneration.

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TDP-43 is an essential DNA/RNA binding protein notorious for its involvement in neurodegenerative diseases, particularly ALS and FTD. Although only a small proportion of ALS/FTD are caused by mutations in the gene encoding TDP-43, nearly all ALS patients and almost half of FTD patients present with TDP-43 pathology. Therefore, it is critical to uncover mechanisms regulating TDP-43 that are perturbed in ALS/FTD to identify potential therapeutic inroads and biomarkers. Due to the high level of overlap between processes known to be regulated by SUMOylation and processes disrupted in ALS/FTD, we hypothesized that TDP 43 may be a target of SUMOylation. We found that TDP-43 becomes SUMOylated rapidly in response to cellular stress upstream of TDP-43 aggregation. To understand the physiological consequences of blocking TDP-43 SUMOylation, we generated a knockin mouse model with a point mutation that prevents endogenous Tdp-43 from being SUMOylated (TDP 43 "SUMO dead" mice). We have also developed a proximity ligation-based assay to monitor TDP-43 SUMOylation in primary neurons, iPSC-derived motor neurons and in human tissue, with the ultimate goal of elucidating roles for TDP-43 SUMOylation in neurodegeneration. Determining the relevance of TDP 43 SUMOylation in

ALS/FTD will help to uncover a novel pathway associated with TDP-43 (dis)function that could ultimately serve as a biomarker or novel therapeutic target for patents with ALS/FTD.

P3-C-603: Binge ethanol exposure of neonatal mice induces long-lasting alterations in the function of anterior thalamic neurons that project to the retrosplenial cortex

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Fetal alcohol exposure produces long-lasting memory deficits, an effect that could be due to damage to components of the posterior limbic memory system, including the retrosplenial cortex (RSC) and anterior thalamic nuclei (ATN). Here, we tested the effect of third trimester-equivalent alcohol exposure (TTAE) on the function of ATN neurons that project to the RSC. We exposed postnatal day 7 (P7) mice to heavy, binge-like ethanol in vapor chambers (blood ethanol level ~0.4 g/dl; ~90 mM). We then injected red retrobeads into the RSC at adolescence (~P60-70) and performed patch-clamp slice electrophysiological recordings from retrogradely labeled neurons in the anterodorsal (AD) and anteroventral (AV) thalamic nuclei 3-4 days later. In AD neurons, TTAE reduced the instantaneous frequency of action potentials. In AV neurons, we observed an interaction between current injection intensity and vapor chamber exposure condition for instant action potential frequency. In AD neurons, TTAE reduced spontaneous excitatory postsynaptic current (sEPSC) frequency and amplitude. In AV neurons, TTAE did not significantly affect the properties of sEPSCs. TTAE increased the total charge of spontaneous inhibitory PSCs (sIPSCs) in AD neurons. These results suggest that TTAE induces long-lasting alterations in the function of RSC-projecting ATN neurons. Ongoing studies are investigating if these functional alterations contribute to deficits in learning and memory associated with fetal alcohol spectrum disorders.

P3-C-604: The neuroprotective effects of optogenetic stimulation of astrocytes in a rat model of neurodegeneration

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Astrocytes comprise a heterogeneous group of glial cells that are intimately involved in numerous functions such as the regulation of oxidative stress and the production of key energy substrates. They are essential in injury and disease response through morphological, physiological and functional changes, in a process known as reactive astrogliosis. Given this, it is unsurprising that astrocytes are altered in Parkinson's disease (PD). For example, the overexpression of α-synuclein in astrocytes is sufficient to produce earlier and more severe motor deficits1. Moreover, the selective targeting and stimulation of astroglia using optogenetics has been shown to stimulate the release of FGF2 and increase functional repair following administration of MPTP and 6-OHDA2. This suggests a neuroprotective effect of astrocytes in PD. We aimed to further investigate the therapeutic potential of astroglia using optogenetics to stimulate astroglial cells in the substantia nigra (SNc) of rats injected with 6-OHDA. Briefly, rats were injected unilaterally with 6-OHDA followed the next day by optogenetic stimulation of

astroglia within the SNc. 21 days post 6-OHDA administration, the rats were tested on several motor behavioral tests. As expected, 6-OHDA lesions induced motor deficits on the apomorphine-induced rotations test. Interestingly, these effects were attenuated with stimulation of SNc astroglia, suggesting an astroglial-induced neuroprotective effect. RNA-sequencing analysis of the SNc revealed differentially expressed genes that are implicated in microglial activation, immune pathways and calcium signaling. Altogether, results from this sequencing analysis further supports the notion that multicellular cross-talk is integral to neurodegeneration and neuroprotective processes.

P3-C-605: Unraveling the role of α-synuclein aggregation in early synaptic dysfunction in Parkinson's disease

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Presynaptic accumulation of misfolded α-synuclein (α-syn) is an early event in the pathogenesis of Parkinson's disease (PD), although its exact role in impaired synaptic function remains elusive. One of the main hurdles in studying the early mechanisms of synaptopathy in PD is the limited spatial and temporal resolution of current models. Our group has developed a new model that mimics the histopathological features of PD, and is based on the use of optogenetics technology named LIPA (light-inducible protein aggregation) that allows for inducing α-syn aggregation in a spatio-temporal manner under the control of blue light. To examine what role LIPA-α-syn aggregates may play in impairing synaptic function we first assessed the activity of striatal cells combining the LIPA model with Ca2+ imaging through mini-endoscopes. Afterwards, we evaluated the presynaptic effects of α-syn aggregates on dopaminergic terminals by analyzing the expression of synaptic markers, as well as the dopamine content using High Performance Liquid Chromatography. Our results revealed a decreased synchronization and frequency of Ca2+ events in striatal neurons shortly after the onset of α-syn aggregation. Moreover, we found increased levels of the presynaptic protein synaptophysin as well as the neurotransmitter dopamine in the striatum of mice with LIPA-α-syn aggregates. Altogether, our data highlight the altered synaptic function as an initial component in the progression of PD. Now, we seek to further understand the mechanisms by which LIPA-α-syn aggregates alter synaptic homeostasis.

P3-C-606: Pain experience of children with Christianson Syndrome

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Children with severe cognitive impairments express pain differently due to difficulties with communication and are unable to self-report pain intensities. This has led to the assumption that children with disabilities/verbal impairments have a higher pain tolerance threshold. To explore this possibility, we recruited fourteen young male participants with Christianson Syndrome (CS) for this study. This X-linked neurodevelopmental disorder is caused by a loss-of-function mutation in the SLC9A6 gene

encoding the cation/proton exchanger NHE6. It is associated with autism-spectrum disorder-like symptoms, including mutism and hyposensitivity to pain. Children with CS were subjected to a novel observational tool, the Pain Sensory and Painful Situations Questionnaire (PSQ) which takes multiple painful situations into account to broaden the description of pain expression. Using social expressive behaviours of pain, the PSQ documented on a "good day", two of the participants likely experienced moderate to severe pain most of the time. Using a mouse model of CS, we observed an increased number of aversive responses to innocuous mechanical stimuli compared to control mice, and a similar result was also seen in our patient cohort. About 30-50% of these patients had an aversive response to normally innocuous stimulation like light touch. Despite that hyposensitivity to different painful situations was present and vocal expression of pain was less prominent in our sample of CS children, our work suggests they may experience chronic or recurrent pain which importantly calls for treatment.

P3-C-607: Axonal fidelity the cerebellar ataxia ARSACS

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An elevated numbers of focal swellings on cerebellar Purkinje cell axons, or torpedoes, have been observed across many neurodegenerative diseases. Modeling suggests that they contribute to the pathophysiology of neurodegeneration. However, our recent findings show that axonal swellings in young, healthy mice enhance axonal propagation in cerebellar Purkinje cells. We wanted to determine what role axonal swellings play in disease. We studied a mouse model of Autosomal Recessive Spastic Ataxia of the Charlevoix-Saguenay (ARSACS), an early-onset form of ataxia. In this model the sacsin gene had been knocked out (Sacs-/-) and they display elevated numbers of Purkinje cell axonal swellings at disease onset. We examined morphological and physiological properties of axons both with and without torpedoes from Sacs-/- and wildtype (WT) mice at disease onset (~P40). Axonal swellings in Sacs-/- mice show significant morphological differences from those in healthy mice. Remarkably, Purkinje cells from Sacs-/- mice without axonal swellings show significant impairment of axonal propagation at disease onset when motor coordination deficits are just detectable. While axonal torpedoes do not worsen propagation deficits, they are unable to restore propagation to WT levels. Our data suggest that axonal swellings observed in Sacs-/- are distinct from those found in healthy mice. Although their appearance may be part of a neuroprotective mechanism, they are unable to counteract the massive axonal propagation failures in Sacs-/- Purkinje cell axons.

P3-C-608: Biochemical and pathological characterization of synuclein aggregates from PD and RBD patient plasma

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Alpha synuclein aggregation is a pathological hallmark of many neurodegenerative diseases known as synucleinopathies including Parkinson Disease (PD), multiple system atrophy and dementia with Lewy

bodies. Recent studies have revealed that synuclein aggregates across synucleinopathies are different in terms of their aggregation kinetics, molecular structures, and pathology. Furthermore, this difference can be seen within PD along its disease course. The aim of this study is to use seed amplification assays to detect and amplify synuclein aggregates within neuronally derived extracellular vesicles in plasma samples from PD and rapid eye movement (REM) sleep behavior disorder (RBD) patients. Since around 80% of patients diagnosed with RBD eventually develop PD within the first two decades, our approach helps us understand synuclein aggregation within PD's disease continuum. Amplified aggregates would be characterized biochemically using proteolytic digestion, circular dichroism, and electron microscopy. Furthermore, the pathology of amplified patient aggregates will be tested using dopaminergic neurons from patient-derived induced pluripotent stem cells. Preliminary results show the successful amplification of synuclein aggregates from biological samples using the real-time quaking-induced conversion assay. Additionally, when synthetic preformed fibrils of alpha synuclein are applied to dopaminergic neurons harboring PD mutations, we detect increased presence of phosphorylated synuclein compared to control. This project will serve as an important platform for the future development of a personalized approach to the diagnosis and treatment of PD patients through non-invasive means by tailoring our approach to the patient's specific specific synuclein aggregation behavior.

P3-C-609: Characterizing the heterogeneity of dopaminergic neurons in the gut using a reporter mouse

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Dopaminergic neurons (DA) synthesize dopamine, a neurotransmitter implicated in motor function and many behavioural processes. In diseases affecting DA neurons (such as Parkinson's disease), mounting evidence underscores the role of the gut-brain axis in its pathogenesis. Earlier investigations of DA neurons in the gut relied on immuno-reactivity to tyrosine hydroxylase (TH)- a rate-limiting enzyme in the production of dopamine. However, there is still ambiguity around the reliability of TH staining as a marker of DA neurons, and the heterogeneity of enteric DA neurons. Our aim; perform a comprehensive characterization of DA neurons across the gut using a reporter mouse expressing a fluorescent molecule under the dopamine transporter promoter (DAT-tdTomato). We conducted multi-parametric immunofluorescence of gut tissues isolated from DAT-tdTomato mice with a defined panel of canonical neuronal and non-neuronal markers to determine the localization and proportion of DA neurons. Our findings reinforce the presence of DA neurons in the gut and that DA neurons are not equally distributed across the gut. We performed scRNAseq of FACS-sorted tdTomato+ cells to reveal novel gene signatures of enteric DA neuronal subtypes. Despite the strides made in describing the transcriptome of various enteric neuron, very little progress has been made in defining DA neurons in the gut. A detailed mapping of their molecular signature will help categorize bona fide enteric DA neurons and infer biological processes that put these cells at risk for neurodegeneration.

P3-C-610: Regulation of the microglial transcriptional landscape in the demyelinating brain

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Multiple sclerosis (MS) is characterized by demyelinating lesions in the brain white and gray matter. Microglia, the resident macrophages of the brain parenchyma, are involved in active MS lesions by contributing to myelin debris phagocytosis and remyelination. This activity is regulated by surface receptors which, upon activation, lead to the binding of transcription factors to genomic regulatory elements, promoting transcription of target genes. However, the regulatory landscape of microglia during demyelination remains under-characterized. To address this issue, we induced demyelination in mice with the cuprizone diet. We then extracted microglia and used FACS to isolate distinct microglial populations based on Cd11b and Cd11c staining. Various massively parallel sequencing methods (i.e., RNA-seq, ChIP-seq, ATAC-seq) were employed to detect differential events in the transcriptome and epigenome. Here we show that microglia's response to demyelination is simultaneously linked to various transcriptional programs. Our RNA-seq analyses indicate that Cd11bHigh microglia are enriched in genes involved in proliferation, while a Cd11c population shows phagolysosome, inflammation, and cholesterol metabolism activity. In addition, the landscape of active promoter-distal regions in the Cd11c population was reprogrammed, with 7180 differentially acetylated sites compared to those of the healthy brain's microglia. Motifs for certain transcription factors (e.g., Egr2, Usf, Mef2a) were differentially enriched in those sites, with Egr2's locus shows demethylation. Our results demonstrate that microglia's transcriptomic and regulatory landscapes are remodeled according to cell population in the demyelinating brain.

P3-C-611: Observing Pleiotrophin-Associated Differential Expression in Ischemic Mice Using RNA Sequencing

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Ischemic strokes greatly contribute to adult deaths and disabilities worldwide and result from a reduction in blood flow to the brain. An emerging approach in ischemic stroke research involves modulating the neuroplasticity of the central nervous system (CNS) to augment recovery post-stroke. One method that this could be done involves counteracting the inhibitory environment induced by chondroitin sulfate proteoglycans (CSPGs) in the CNS's extracellular matrix. A neurotrophic growth factor called pleiotrophin (PTN) can interact with CSPGs to promote pro-growth processes, and thus may be effective in reducing inhibition after stroke to promote adaptive plasticity and recovery. However, the degree to which PTN induces growth-related signaling in strokes remain unknown. In the present study, we utilized mRNA and miRNA sequencing to observe differential expression in PTN-associated pathways in a mouse model of stroke. Photothrombosis was used to induce ischemic strokes in adult C57BL6/J mice, after which the mice received cortical microinjections of either PTN or saline as a control. One week after stroke induction, the mice were euthanized, and RNA was extracted from brain and spinal cord tissue and sent to Genome Quebec for sequencing. We hypothesize that administering PTN in mice with ischemic strokes will result in an upregulation in genes related to pro-growth pathways. The insights

gained from this study may either generate new targets or validate targets implicated in previous studies, and can guide future studies on PTN's exact role in post-stroke neuroplasticity.

P3-C-612: Exploring the consequences of perturbed TDP-43 SUMOylation in vivo: implications for ALS-FTD

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Annually, thousands of Canadians are diagnosed with and die from Amyotrophic Lateral Sclerosis (ALS), a progressive neurodegenerative disease characterized by motor neuron loss. Patients suffer motor impairments and typically die from respiratory failure 2-5 years after diagnosis. Interestingly, ALS is on a disease continuum with Frontotemporal Dementia (FTD) where selective loss of cortical neurons produces diverse behaviour changes including deficits in executive and social skills. Connecting these diseases is TDP-43 (encoded by TARDBP), an essential DNA/RNA binding protein critical to cellular functioning. Importantly, nuclear-to-cytoplasmic mislocalization of TDP-43 is a pathological hallmark of most ALS-FTD cases despite mutations in TARDBP constituting few familial forms. Therefore, identifying factors that regulate TDP-43 may thus uncover therapeutic targets to rectify pathology and disease. While TDP-43 is known to be ubiquitinated and phosphorylated in disease, our lab recently found TDP-43 is SUMOylated in response to stress. To understand how disrupting this may contribute to ALS-FTD pathogenesis, we developed a TDP-43 "SUMO dead" mouse allele. Longitudinal characterization of the model is being done at biochemical, histological, and behavioural levels to investigate in vivo consequences of loss of TDP-43 SUMOylation; ultimately determining if these mice recapitulate ALS-FTD phenotypes. Early results suggest cognitive changes and TDP-43 pathology in line with disease states, highlighting the need to further understand this process as it relates to ASL-FTD.

P3-C-613: Tinospora cordifolia improves oxidative stress-mediated mitochondrial dysfunction against rotenone-induced PD mice

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Background: Oxidative stress-induced mitochondrial dysfunction and disturbed mitochondrial dynamics were found to be common phenomena in the pathogenesis of Parkinson's disease (PD). Tinospora cordifolia (Guduchi) has emerged as a novel medicinal plant that protects neurons from oxidative stress. Objective: In this study, we investigated the neuroprotective effects of Tinospora cordifolia on mitochondrial dysfunction and the underlying mechanisms in classic rotenone-induced Parkinsonism. Material and Methods: Mice were divided into four experimental groups: control, rotenone (2 mg/kg body wt., subcutaneous), Tinospora cordifolia extract (TCE, 200 mg/kg body wt., oral) + rotenone, and TCE only]. Mice were pre-treated with TCE for a week and then simultaneously injected with ROT for 35 days. Results: TCE administration significantly improved locomotor performance and increased tyrosine

hydroxylase expression in the substantia nigra pars compact of rotenone-intoxicated mice. Furthermore, TCE improved mitochondrial dysfunction via counteracting the decline in mitochondrial electron transport chain complex activity evoked by ROT. Similarly, TCE suppressed ROT-induced imbalance of the Bax/Bcl-2 ratio and activation of caspase-3. Discussion and Conclusion: This study demonstrates the neuroprotective effects of TCE against rotenone-induced apoptosis in mice. The Bax/Bcl-2 ratio, mitochondrial dysfunction, and expression of caspase-3 were seen to be significantly increased on rotenone-intoxication. However, TCE was potent in protecting the neurons against rotenone-induced cytotoxicity through the regulation of oxidative stress-mediated mitochondrial dysfunction and apoptosis in the mouse model of PD.

P3-C-614: Generation of oligodendrocytes from patient-derived induced pluripotent stem cells (iPSCs)

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In the CNS, oligodendrocytes are responsible for the myelination of axons and are involved in various neurological diseases. The limited access to human oligodendrocytes from patients is a major obstacle for disease modeling. Induced pluripotent stem cells (iPSCs) are genetically reprogrammed stem cells that can self-renew indefinitely in vitro and differentiate into all cell types. A number of protocols have been published to differentiate oligodendrocytes from iPSCs, but are rather difficult and require long differentiation periods (56 to 147 days) according to the current published protocols. OBJECTIVES: The aim of the project is to generate iPSC-derived oligodendrocytes from patients with neurological disorders (Leukodystrophies, Ataxias, Amyotrophic lateral sclerosis) and to develop a co-culture model of iPSC-derived oligodendrocytes with motor neurons in order to better study the interaction between these two cell types in health and diseases. METHODS: iPSC lines derived from patients' cells carrying specific known mutations will be produced and characterized. The iPSCs will then be differentiated into oligodendrocytes. Immunofluorescence (IF), RNA-seq and qPCR analyses will be used to evaluate the terminal differentiation potential of oligodendrocytes and to characterize their gene expression profiles. RESULTS: Our analyses showed that the generated oligodendrocytes express mature oligodendrocyte markers after only 28 days of culture, in addition to promoting motor neuron myelination in a tissue-engineered 3D co-culture model. CONCLUSIONS: A rapid and efficient protocol for the generation of oligodendrocytes is key for disease modeling and to better understand neuropathological mechanisms associated with demyelinating diseases and high-throughput drug screens.

P3-C-615: 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 heterogeneous disorder that likely involves a concoction of genetic risk factors, environmental exposures, and aging. Despite recent advances in understanding the genetics of PD, there remains a gap in our understanding of how genetics interact with environmental factors. Understanding how gene-environment (GxE) interactions conspire to regulate α-synuclein (αSyn), a key dysregulated hallmark in PD, is important to understand the initial steps that lead to pathogenesis. We have developed a fluorescent-based system to test complex GxE interactions in a high-throughput manner to reverse engineer this feature of disease. We identified 26 environmental factors epidemiologically linked to PD. After identifying ideal subtoxic doses, we exposed wild-type primary mouse cortical neurons to binary combinations of each dose (~700 combinations). We found multiple combinations that resulted in altered αSyn metabolism. Building off this initial dataset, we are exposing genetically sensitized backgrounds (e.g. Snca, Lrrk2 and Gba PD-linked mutants) to determine αSyn altering combinations by high-content imaging. Then, we will validate hits by performing both dose-responses and time-courses. We will further explore top hits in increasingly physiologically relevant milieux and explore the mechanisms whereby these GxE interactions influence αSyn. Ultimately, we will confirm these findings in vivo to study how GxE converge on PD pathology. This project will help uncover complex relationships between GxE interactions and PD pathogenesis.

P3-C-616: Altered m6A RNA methylation in the brain of humans with depression

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Epigenetic mechanisms, which are altered in response to environmental factors, are known to be involved in the pathophysiology of MDD; however, little is known about the impact of the epitranscriptome. In recent years, RNA modifications have emerged as a crucial mechanism in the post-transcriptional regulation of gene expression. Emerging evidence suggests that N6-methyladenosine (m6A) plays an important role in the brain, including neurogenesis, and memory and learning. Moreover, recent studies have linked m6A to molecular and behavioral responses to stress, making it an important candidate regulator of stress-related psychiatric disorders, including MDD. This study aims to describe the landscape of m6A in the ventromedial prefrontal cortex and to identify changes that may occur in the context of MDD. Using m6A-seq, we identified ~20,000 m6A peaks in the human brain, and these peaks enriched the known m6A consensus motif "GGAC" and 3'UTR and coding region as suggested by previous studies. These m6A-tagged genes are related to neuronal and synaptic regulation confirming that m6A plays a vital role in brain function. Our differential methylation analysis shows a distinct m6A profile in MDD and control, with little overlap between males and females. These differentially methylated genes were enriched for synaptic function in both males and females with MDD. Our results highlight a significant role of m6A in MDD, possibly by adjusting the function of the synaptic-related genes.

P3-C-617: Cell-type Chromatin Accessibility Changes in Major Depressive Disorder.

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Research Problem: Major Depressive Disorder (MDD) is the leading cause of lifelong disability and a major risk factor for suicide. Genome-wide association studies (GWAS)-identified genetic variants for psychiatric disorders are disproportionally located in the non-coding regions of the genome. Objectives: a) To identify cell-type specific gene-regulatory changes and transcription factors motifs (TFs) disrupted by MDD genetic variants. Methodology: Using high-throughput snATAC-seq (Single Nucleus Assay for Transposase- Accessible Chromatin using Next Generation sequencing), we sequenced accessible regions of the genome in more than 200k nuclei from 44 MDD individuals and 44 age- and sex-matched healthy individuals. Results: The majority of differential accessibility changes in MDD cases were found in microglial (58%), deep-layer excitatory neuronal (21%), astrocytic (%) subtypes. Early-response and neurodevelopmental transcription factors (TFs) showed increased motif accessibility and target gene expression in deep-layer excitatory neurons and glucocorticoid response element motifs in an astrocytic subclusters, while canonical microglial transcription factors, such as (PU.1, IRF8) showed decreased accessibility in cases. In addition, MDD heritability enriched in the deep-layer excitatory neuronal cluster that showed chromatin accessibility changes. Further, gapped-kmer SVM was trained to identified MDD SNPs showing allele-specific changes in chromatin accessibility at TF motif binding sites, many of which were found to be differentially accessible in MDD cases. Future Directions: Using allelic-imbalance analysis and gene reporter assays, we will validate allele-specific chromatin accessibility changes exhibited by prioritized MDD SNPs.

P3-C-618: Development of a behavioral biomarker for cognitive impairment using navigation in virtual reality

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There is a critical need for non-invasive, inexpensive, and reliable methods to detect individuals with pre-clinical Alzheimer's disease (pre-AD). AD in its early stages damages brain regions involved in spatial navigation and route planning. This reduces performance in spatial navigation using both egocentric and allocentric strategies - however, these impairments are hard to distinguish from those caused due to normative aging. We developed a behavioral test to examine the navigation performance of participants, using a 'corridor maze' in an immersive 3D virtual reality (VR) environment. Participants will navigate this space using a joystick and a VR headset and perform orienting tasks with graded complexity. We will quantify their egocentric and allocentric errors as a function of complexity, parameterized by the length and turns of the route. We will quantify a boundary in the error-complexity space at which the performance drops, which will be a characteristic profile that we will compare between young and older healthy participants. Once we define the profile for normative aging, we will test participants with preclinical AD to identify specific cognitive impairments that may be indicative of early AD-related neurodegeneration. These human trials will be paired with rodent electrophysiological trials in a similarly structured physical maze apparatus, enabling cross-species comparisons, revealing population responses in the hippocampal formation responsible for the functional impairments we observe in humans.

P3-C-619: Using Transcranial Magnetic Stimulation to Investigate the Acute Effects of Translingual Neurostimulation in Individuals with Multiple Sclerosis

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Introduction: Non-invasive neuromodulation techniques have emerged as a promising treatment to facilitate rehabilitation for individuals with Multiple Sclerosis (MS). One neuromodulation method, translingual neurostimulation (TLNS), involves electrical stimulation of the tongue. Paired with physiotherapy, TLNS improves motor function in individuals with MS. Despite preliminary findings supporting the benefits of TLNS and physiotherapy, the actual mechanisms underlying TLNS is not known. Functional brain imaging devices such as transcranial magnetic stimulation (TMS) can help elucidate how TLNS may work to influence plasticity and recovery. Methods: Participants (n=24) were recruited from a clinical trial in which individuals with MS were randomized to receive either a real or modified TLNS device combined with physiotherapy for gait and balance. TMS variables, including resting motor threshold (RMT), active motor threshold (AMT) and recruitment curve (REC) were measured pre and post a 20-minute TLNS treatment. Results: A repeated measures ANOVA using mixed models was conducted to investigate differences in corticospinal excitability pre and post TLNS treatment between the real and sham treatment groups. Comparing pre and post AMT and REC values, there were no significant differences in maximum stimulator output (%MSO), motor evoked potential (MEP) amplitude or cortical silent period (CSP) between the real and sham groups ($p>0.1$). Conclusion: Our preliminary examination of TMS variables, AMT and REC, indicate that 20 minutes of TLNS did not increase corticospinal excitability in individuals with MS. Future research will use functional near infrared spectroscopy to interrogate overall brain activation through changes in cerebral blood flow.

P3-C-620: CFTR Modulators Failed to Correct Sensory Neuron Impairment in CFTR-ΔF508 Mice

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Cystic Fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) protein. The deletion of the amino acid phenylalanine at position 508 (△F508) is the most prevalent mutation of the disease. CF results in severe respiratory and digestive symptoms that have historically limited the life expectancy of patients. Fortunately, current therapeutic advances allow many patients to survive well into adulthood. Combination therapy of the CFTR modulators elexecaftor, tezacaftor and ivacaftor (ETI) have been successful in treating the pulmonary symptoms of CF. Consequently, older patients experience long-term effects of the disease, such as peripheral neuropathy. Our preliminary observations in sensory neurons from the dorsal root ganglion (DRG) of CFTR-/- swine showed disrupted chloride homeostasis and reduced excitability. To understand the relevance of these findings to CF in humans, we use here DRG neurons from △F508 mice to investigate chloride homeostasis, neuronal excitability, and the possible effect of the ETI treatment. For chloride homeostasis, we measured the internal chloride levels using the MQAE dye and found that chloride homeostasis was impaired. More importantly, the ETI

treatment failed to correct chloride levels. To evoke action potential, we injected incremental steps of depolarizing current (100 pA, 500ms) and found that DRG neurons of △F508 mice had reduced action potential frequency, which did not improved by the ETI treatment. Taken together, our data provides new insight in the mechanisms underlying sensory neuropathy in CF, and suggest that CFTR modulators may be less effective in extra-pulmonary targets.

P3-C-621: Porphyromonas gingivalis infection in Down Syndrome individuals and its possible role in neurodegeneration

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Individuals with Down Syndrome (DS) have a high susceptibility to developing chronic periodontitis and early Alzheimer's disease (AD)-like dementia. Importantly, periodontitis has been defined as a risk factor for AD. Phorphyromonas gingivalis, a periodontopathogenic bacterium, and its gingipains (virulence factors) have been found in AD brains. P. gingivalis is also highly prevalent in DS individuals from early childhood and, moreover, young DS adults (less than 40 years) show a unique and exacerbated neuroinflammatory profile before developing dementia. Therefore, a brain bacterial colonization could initiate a vicious cycle of deleterious inflammation triggering early and chronic neurodegeneration in this population. The main goal of this work is to determine whether P. gingivalis infection is related to neuronal degeneration in DS. We analyzed post-morten DS brains using immunofluorescence and biochemistry techniques. We identified P. gingivalis and its gingipains in DS brains at different ages. We observed a correlation between the presence of P. gingivalis and B-amyloid accumulation, with neurons from young DS individuals showing perinuclear gingipain accumulation and nuclear condensation. High neurodegeneration, glial reactivity, extracellular DNA, and astrocytic polarization were detected in individuals over 40 years. Infected cells were also observed in control individuals but at a lower level than in DS individuals. These results suggest that P. gingivalis brain infection could alter brain homeostasis producing neuronal and glial cell dysfunction which can contribute to neuronal death in DS individuals.

P3-C-622: ZDHHC8 isoforms are selectively expressed in excitatory and inhibitory neurons and their cell-type ablation leads to behavioural abnormalities relevant to schizophrenia and autism

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Deletion of the palmitoyltransferase, ZDHHC8, has been linked to various neurodevelopmental disorders such as schizophrenia and autism. One of the prevailing theories of the biochemical mechanism underlying these disorders is an imbalance in excitatory and inhibitory signaling. Using single-cell RNA sequencing data, we identified two major transcript variants of ZDHHC8 that are conserved across mammalian species and have divergent patterns of expression in excitatory and inhibitory neurons. We confirmed this pattern of cell type-specific isoform expression by assessing the co-localization of variant-

targeted fluorescent in situ hybridization probes with excitatory and inhibitory neuron-specific transcripts. To ascribe function to these different isoforms, we conditionally ablated zdhhc8 in excitatory or inhibitory neurons (thereby predominantly ablating the excitatory or inhibitory variant, respectively) using the cre-loxP system. We observed sex-specific and neuron subtype-specific differences in motor coordination, prepulse inhibition, sociability and socialization. Further work is required to determine the role of ZDHHC8 isoforms in the proper functioning of excitatory and inhibitory neurons. However our work shows that disrupting either ZDHHC8 isoform can phenocopy behaviours observed in patients with schizophrenia and autism.

P3-C-623: Increase in nucleus accumbens activity during social interaction is absent in Cntnap2-null and Fmr1-null mice

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Autism Spectrum Disorder (ASD) is a heterogeneous condition with varying subtypes including monogenic syndromes that account for ~20% of all ASD cases. A clear link between the gene mutations and behavioural symptoms remains unclear. Finding convergent neuronal mechanisms between these conditions is needed to resolve effective treatment strategies. Cortical Dysplasia-Focal Epilepsy and Fragile X syndrome, caused by a loss of the Cntnap2 and Fmr1 gene respectively, are monogenic subtypes for which mouse models are well developed. One major phenotype of both models is reduced sociability, which is a core ASD symptom. The nucleus accumbens (NAc) is an integrative area that translates social motivation into action and shows increased activity during social interaction. We hypothesized that due to their low sociability phenotype, both Cntnap2-null and Fmr1-null mice will show no increase in NAc activity post-social interaction. To test this, we performed a social interaction task with a novel mouse, and Fos-immunostained NAc brain slices from experimental mice to assess changes in neuronal activity. Both mutant mouse lines showed no increase in Fos-postive cell density in the NAc after social interaction, unlike WT mice (n=8, 3 sections/n). Since the NAc is a key part of the reward pathway, these data suggest a lack of social reward in these mice that could explain their reduced sociability phenotypes. Additionally, these data reveal a regional overlap in aberrant activity between the two mouse models, providing a basis for further investigation of the NAc as a treatment target for social symptoms in monogenic ASD subtypes.

P3-C-624: Phase-amplitude coupling in response to social and non-social stimuli in the 5xFAD mouse model of Alzheimer's disease

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The 5xFAD mouse model of Alzheimer's disease exhibits a number of cognitive, behavioural, and physiological impairments concomitent with neuropathology. Specifically, we have previously identified altered social behaviours by 6 months of age in female and male transgenic 5xFAD mice. Evidence suggests that mouse models of Alzheimer's disease (including the 5xFAD mouse model) generally exhibit

altered phase-amplitude coupling. Additionally, altered phase-amplitude coupling has been linked with social deficits in a mouse model of autism; however, it is unclear what role altered neural activity plays in mediating social deficits in Alzheimer's disease. The present study uses a custom-built olfactometer to deliver social and non-social stimuli to awake, behaving mice, during which local field potentials are recorded. Preliminary results suggest that wild-type 5xFAD mice exhibit differential phase-amplitude coupling in response to social vs non-social stimuli. This work has implications for understanding factors underlying behavioural and psychological symptoms of dementia in individuals with Alzheimer's disease.

P3-C-625: Role of neutrophil-induced collateral and microcirculatory failure in futile recanalization in a mouse model of ischemic stroke

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In ischemic strokes, blood flow is blocked in the brain vessels, and current treatments aim to reopen the blocked vessels (termed recanalization), restoring blood flow to the ischemic brain tissue (termed reperfusion). Despite successful recanalization, these treatments do not always result in complete reperfusion or a good outcome, with over half of stroke survivors still disabled. Such recanalization without good outcome is known as 'futile recanalization.' We investigated how collateral failure and microcirculatory failure contribute to futile recanalization. A filament middle cerebral artery occlusion (MCAo) model was performed in both young and aged C57BL/6 mice of both sexes. High resolution imaging of blood flow dynamics in collaterals and small capillaries below the cortical surface demonstrated decreased vessel diameter, flow velocity, RBC flux, and capillary flow, and this will be quantitatively correlated with infarct size and blood biomarkers. After complete MCA recanalization in mice, large areas of the capillary bed do not reperfuse within 24h, indicating microcirculatory failure. Imaging data further showed neutrophil accumulation in ischemic capillaries, and improved flow after neutrophil depletion, suggesting this adhesion might be responsible for microcirculatory failure. As compared with young adult mice, neutrophil-induced microvasculature blockage was more noticeable in aged mice. Our findings suggest that strategies to enhance collateral flow and modulate neutrophil stalls in microvessels could prevent futile recanalization and improve stroke outcomes. Keywords: Ischemic stroke, Futile recanalization, Collateral flow, Microcirculation, in vivo imaging

P3-C-626: Patterns matter: phasic locus coeruleus activation rescues spatial and olfactory discrimination in a pre-tangle tau rat model

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INTRODUCTION: The earliest abnormality associated with Alzheimer's disease (AD) is the presence of abnormal phosphorylated pre-tangle tau in locus coeruleus (LC) neurons. Human brain studies reveal that pre-tangle tau in LC neurons spreads to other brain regions resulting in memory loss and cognitive decline. Importantly, LC neuronal activity pattern is related to its spiking modes: phasic and tonic. Using

an animal model that captures the features of human pre-tangle tau, we ask if LC spiking patterns influence the course of pre-tangle tau. OBJECTIVE: To study the relationship between LC neuron activity, life patterns, and AD progression. METHOD: We infused a pre-tangle human tau gene producing tau pseudo-phosphorylation on 14 sites characteristic of human pre-tangle tau, together with a light-sensitive excitatory ion channel, into the neurons of LC. We provided daily phasic or tonic optogenetic activation patterns to LC neurons for six weeks in mid-adulthood and probed cognitive and anatomical changes. RESULT: LC phasic stimulation prevented spatial and olfactory discrimination deficits and reserved LC axonal density. A high tonic activation pattern increased indices of anxiety- and depression-like behavior, did not improve cognition, and worsened LC neuronal health. CONCLUSION: Our results suggest that variations in the activation patterns of the LC induced by environmental experiences could account for individual differences in susceptibility to AD development. We show that the activity patterns of the LC play an essential role in cognitive health, and novelty-related phasic LC activation can reverse the harmful effect of pre-tangle tau.

P3-C-627: Microglial core properties impaired after injury in the developing brain

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Background: Extreme preterm infants are exposed to multiple inflammatory stressors including perinatal cerebellar hemorrhage (CBH) and postnatal infection, two major risk factors for neurodevelopmental impairments. Microglial core properties will be assessed to further characterize the impact on microglial cells function in the pathogenesis of cerebellar injury during development. Methodology: Mice were exposed to CBH at postnatal day 2 (P2) combined or not with early inflammation (LPS). Microglia phenotypic changes across time (P2, P3, P7 and P15) were analyzed by flow cytometry using a panel of markers. Residual phagocytosis capacity of microglial cells was analyzed using a standardized bead assay and immunostaining techniques. Results: Our data showed that two weeks after being exposed to perinatal insults (P15), cells featuring M2 phenotypic profile are significantly decreased in mouse pups exposed to a systemic inflammatory stress alone (LPS: 10,88%, *P=0.040, n=7) or exposed to combined insults (CBH+LPS: 11,31%, *P=0.039, n=8) compared to controls (29,02 %, n=7)translating anomalies in tissue repair function. Primary cell culture of microglia exposed to insults showed a very low residual phagocytic capacity from all exposure groups (median<0.000% [0,0],****P<0,0001) compared to controls (0,512% [0,1]). Conclusions: Perinatal insults exposure alters tissue repair and core properties of microglial cells post-injury, which translate to altered microglia proliferation and tissue remodeling responses and may create a vulnerability window during the recovery phase of injury.

P3-C-628: Next-Generation Humanized Mice to Investigate Traumatic Brain Injury's Interaction with APOE4, the Strongest Genetic Risk Factor for Dementia

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Traumatic brain injury (TBI) is a leading cause of disability and has been linked to Alzheimer's disease (AD). Patients with a history of TBI can present with pathologies similar to the three pathological hallmarks of AD: Amyloid protein plaques, Tau Protein tangles, and chronic inflammation. Apolipoprotein E4 (ApoE4) is the strongest genetic risk factor for AD and is involved in all three AD hallmarks, while also being associated with worse outcomes after TBI. We hypothesize that TBI triggers the pathological processes underlying AD development and accelerates AD progression in a manner that is exacerbated by the APOE4 allele. To explore this, we used transgenic mice carrying three wildtype human genes: 1) Amyloid precursor protein (hAPP), 2) microtubule-associated protein Tau (hMAPT), and 3) Two copies of either ApoE4 or ApoE3 control. Half of the mice experienced three clinically translatable non-invasive mild TBIs, modeled after human concussions, while the rest underwent a sham procedure. All mice were evaluated using the Continuous Performance Task (CPT), a test of attentional processes widely used with AD patients. CPT is conducted at 6 and 12-month timepoints post-injury, accompanied by molecular analyses to characterize the timing and severity of AD pathology. No differences were observed between the genotypes and sexes at the baseline before TBI. We will report our early results from the 6-month post-injury timepoint in this study. This study aims to help explain how APOE4 and a history of TBI may interact to increase the susceptibility to dementia.

P3-C-629: Adult neurogenesis in neurodegenerative disorders and following long-term treatment with deep brain stimulation of the subthalamic nucleus

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This study aimed to examine adult neurogenesis in patients who suffered from Huntington's disease (HD) and Parkinson's disease (PD), as well as in PD patients who received long-term treatment by deep brain stimulation (DBS) of the subthalamic nucleus. Quantitative analysis of post-mortem brain sections immunostained for specific cell-type markers such as proliferating cell nuclear antigen (PCNA), glial fibrillary acidic protein (GFAP) and doublecortin (DCX) were performed in the subventricular zone (SVZ) and the adjacent caudate nucleus. Our results indicate a significant increase in the thickness of the SVZ, along with an increased density of proliferating and activated stem cells (PCNA+/GFAP+) in the brain of HD patients and PD patients treated with DBS, compared to matched controls. We also observed a significant increase in the density of immature neurons (DCX+) in the SVZ and the caudate nucleus of HD brains. The DCX+ cells observed in the caudate nucleus of HD brains were characterized by extended processes, when compared to those found in the SVZ. Overall, our data indicate that the number of dividing stem cells and newly generated neurons is significantly increased in HD as well as in PD patients who received long-term DBS treatment. This increased cell proliferation can be viewed as a compensatory mechanism designed to cope with the neurodegenerative processes at play in HD. They also indicate that long-term DBS of the subthalamic nucleus might restore SVZ cell proliferation that is known to be reduced in PD.

P3-C-630: Synaptic alterations at the lateral habenula neuronal outputs in the chronic social defeat stress model

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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 serotonergic 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 activate LHb efferents, 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 mice while no change was observed for PPR. Also, we found a decreased intrinsic activity in VTA projecting LHb neurons and an imbalance in the excitatory-inhibitory inputs to the VTA- and RMTg-projecting LHb neurons.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.

P3-C-631: Genetic modulators of alpha-synuclein propagation in Parkinson's disease: a genome-wide CRISPR approach

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One of the hallmarks of Parkinson's Disease (PD) is the presence of Lewy bodies, which are comprised of protein aggregates including α-synuclein (αSyn). Lab-generated preformed fibrils (PFF) of αSyn, modelling pathological fibrils in patients, have been shown to propagate transcellularly between neurons, which is thought to contribute to their toxic effect. While many pathways have been suggested to play a role in the internalization and propagation of αSyn aggregates, our understanding of the mechanisms remains limited. To determine the genes, pathways, and mechanisms that are critical for fibril internalization and propagation in PD, we performed CRISPR activation genome-wide screens on PFF accumulation. We identified putative modulators of αSyn fibril uptake and confirmed their effect using flow cytometry and high-content microscopy. This screen yielded distinct genetic, druggable targets, which are suggested to be involved in inflammation, endo-lysosomal trafficking, and protein glycosylation. Selected genes will be further validated using stem-cell derived human neurons to provide

a physiologically relevant glimpse into the mechanisms of αSyn accumulation. This research will shed light on the function of genes that are important in the spreading of αSyn fibrils. Identifying novel genetic targets will then allow for development of therapeutics, combating PD symptoms and/or halting disease progression.

P3-C-632: Spatially resolved single-cell profiling of the murine brain reveals a multicellular response to chronic neonatal hypoxia

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Diffuse white matter injury (DWMI) is a major cause of neurodevelopmental disorders in preterm infants. As a result of their immature respiratory system, preterm infants are exposed to low oxygen levels, or hypoxia (HX), which can damage and impair the development of the brain's white matter (WM). However, the cellular mechanisms that govern the perinatal brain's response to DWMI remain poorly understood. Here, we leveraged a tool for spatially resolved single-cell transcriptomics (MERFISH) to investigate how neonatal HX affects the brain's spatial organization and signaling landscape. We used a well-established mouse model of neonatal HX-induced DWMI, in which mice are exposed to 10% oxygen from P3-P11, and performed MERFISH at P21, during the recovery period. Over 549,000 cells were profiled across 3 HX-exposed mice and 3 normoxia (NX)-exposed control mice. A custom panel of 500 genes allowed the identification and spatial mapping of diverse cell types, cell states, and anatomical regions within the forebrain, revealing changes in molecular and spatial signatures, and altered cell-cell interactions across the HX brain. Notably, we observed increased differentiation-primed oligodendrocyte progenitor cells (OPCs) and unique OPC-immune cell interactions within the HX cortex, suggesting an important role for immune signaling in mediating WM regeneration. Together, these results provide novel insights into the mechanisms of WM regeneration in the perinatal brain and show that complex multicellular processes underlie the brain's regenerative response to hypoxia-induced DWMI.

P3-C-633: Uninterrupted in vivo cerebral microdialysis measures of the acute neurochemical response to a single or repeated concussion in a rat model combining force and rotation.

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There are marked alterations in extracellular amino acid levels following a concussion, contributing to delayed neuronal damage, but the consequences of repeated concussions prior to complete recovery are less known. This study investigated in adult rats, acute changes from a single or repeated concussive trauma. A weight-drop injury model and in vivo cerebral microdialysis were used. Primary outcome includes amino acid levels and secondary outcome includes righting time. Samples were taken in 10 min increments for 60 min prior to, during and for 60 min following impact, and analyzed for glutamate, GABA, taurine, glycine, glutamine, and serine using HPLC. For repeated concussion cases, a second injury

was induced 60 min after the first, and 6 additional samples were collected for 60 min. Following the first concussion, glutamate, taurine, and glycine levels as well as righting times and excitotoxic indices were significantly increased compared to sham injured animals. Following the second concussion, glutamate and taurine levels were significantly increased again, albeit only halfway, compared to sham injured animals. Righting times took significantly longer after the second concussion, while glycine levels were comparable to sham injured animals. These results suggest that single and repeated concussion induce an acute increase in certain amino acids. While these changes were less pronounced following a second impact, neurological symptoms as seen through righting times had worsened, suggesting acute cumulative effects of repeated concussion on neurological function.

P3-C-634: ALS dermal fibroblast-derived exosomes increase wound healing

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease leading to paralysis and death in patients 2 to 5 years after onset. Developing therapies for ALS becomes difficult as the disease is already well established and thus difficult to treat following clinical 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. Since then, other observations have been made linking skin tissue abnormalities in ALS 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 therefore hypothesised that ALS dermal fibroblast-derived exosomal cargo could also increase would healing. Exosomes from healthy, ALS and neuronal control patients were isolated and characterized. Scratch test assays were performed using dermal fibroblasts isolated from ALS patients and healthy controls. Exosomal content was assessed by mass spectrometry and network analyses using Ingenuity Pathway Analysis (IPA).ç A significant increase in cell migration was observed when adding ALS patient-derived exosomes on monolayered scratched wild-type cells. Mass spectrometry and IPA analyses revealed that the studied exosomal proteins were more associated with Gene ontology biological functions such as ECM formation and cellular migration. These findings reveled a novel exosome-dependant ECM deposition mechanism and suggest that the use 3D-fibroblast cellular culture may emerge as an innovative approach in precision medicine to study the role of exosome and patient derived ECM proteins in ALS.

P3-C-635: Exosomes derived from dermal fibroblasts haploinsufficient for neurofibromin enhance angiogenesis in a neurofibromatosis type 1 model

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Introduction: Neurofibromatosis type 1 (NF1) is a neurogenetic genetic disorder with many clinical manifestations. Patients can develop neurofibromas, which are highly vascularized benign tumors that can undergo malignancy. However, neurofibroma's morphogenesis still remains poorly understood.

Interestingly, it has been shown that NF1 patient's dermal haploinsufficient (+/-) fibroblasts, cultured in three-dimension (3D), enhanced cutaneous neurofibroma formation in vitro. Thus, we hypothesized that exosomes secreted by NF1 +/- fibroblasts carry pro-angiogenic signals and play a crucial role in neovascularization and modification of the tumoral microenvironment. Methods: Endothelialized tissue-engineered reconstructed skins were generated using control and NF1 patient's fibroblasts and microvascular endothelial cells (MVEC). Total exosomal proteins, isolated in conditioned cultured media, were purified and analyzed by mass spectrometry (LC-MS/MS). Tube formation assay using Matrigel® was also used to measure angiogenic properties of exosome proteins secreted by NF1 fibroblasts. Results: Mass spectrometry analysis revealed that 99 proteins were significantly modulated in NF1 +/- fibroblast-derived exosomes, several of them fulfilling a role in angiogenesis in silico. Moreover, NF1- exosomes highly enhanced tube formation while co-cultured with MVECs. Conclusion: Our study suggests that haploinsufficiency of the NF1 gene alters the exosomal cargo secreted by dermal fibroblasts to create a pro-angiogenic microenvironment favouring cutaneous neurofibroma formation.

P3-C-636: Manipulating KCC2 delays disease progression and prolongs survival in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder that affects the upper and lower motor neurons in the CNS. Hyperexcitability in the spinal cord is a feature of ALS during its pre-symptomatic phase. While the substrates of this hyperexcitability can be many, recent studies have identified a particularly interesting new target: the CNS-specific potassium-chloride cotransporter, KCC2. Aberrant KCC2 function underlies several syndromes associated with disrupted inhibition, including epilepsy, motor spasticity, schizophrenia and autism. Patients with the sporadic form of ALS have shown a downregulation of the gene SCL12A5, which encodes KCC2. A recent study found a decrease in short-interval intracortical inhibition preceding hyperexcitability in pre-symptomatic ALS patients, suggesting deficits in inhibitory synaptic transmission. We hypothesized that a loss of KCC2 underlies hyperexcitability and ensuing excitotoxicity leading to motoneuron degeneration in ALS; enhancing KCC2 function will restore normal excitability and prevent this neurodegeneration. Here, we show that KCC2 is reduced in the brain and spinal cord of ALS mice and patients with ALS. Using KCC2-enhancing compounds, we were able to restore KCC2 expression and function in ALS mice, which dramatically delayed the onset of motor deficits and extended the lifespan of ALS mice. Finally, acute treatment of KCC2-enhancing molecules restored KCC2 expression in a patient-derived iPSC line with the SOD1 mutation. Results from these experiments hold great therapeutic potential.

P3-C-637: Multiplex, single-cell CRISPRa screening for cell type specific regulatory elements

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CRISPR-based gene activation (CRISPRa) is a promising approach for gene therapy, but ideally would enable specific genes to be upregulated in a cell type-specific manner, e.g. as might be mediated by its targeting of enhancers. Here, we describe an experimental framework that combines highly multiplexed perturbations with single-cell RNA sequencing (sc-RNA-seq) to identify cell-type-specific, CRISPRa-responsive cis-regulatory elements and the gene(s) they regulate. Random combinations of many gRNAs are introduced to each of many cells, and cells are computationally partitioned into test and control groups to test for effect(s) of CRISPRa perturbations of both enhancers and promoters on the expression of neighboring genes. Applying this method to regulatory elements of neurodevelopmental disorder risk genes in both K562 cells and iPSC-derived neurons, we identify gRNAs capable of specifically and potently upregulating target genes. A consistent pattern is that the "sensitivities" of individual enhancers to CRISPRa are consistently restricted by cell type, implying a dependency on either chromatin landscape and/or additional trans-acting factors for successful gene activation. We are currently applying this approach to large-scale screens of distal cis-regulatory element-targeting gRNAs that activate haploinsufficient neurodevelopmental disorder risk genes in a cell type-specific manner.

P3-C-638: Altered neuroimmune response following TLR4 or TLR7/8 activation in male and female rats exposed to alcohol prenatally

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Prenatal alcohol exposure (PAE) leads to immune system dysfunction and increased susceptibility to autoimmune diseases. To explore potential mechanisms by which PAE induces immune dysfunction, the current study examined the impact of PAE on toll-like receptor 4 (TLR4) and TLR7/8 activation. Pregnant rats were divided into PAE - liquid ethanol diet ad libitum and CON - pelleted control diet ad libitum. Male and female offspring were challenged in adulthood with LPS (40 µg/kg; activates TLR4), R848 (1 mg/kg; activates TLR7/8) or DMSO (vehicle) followed by blood and brain sample collection to measure cytokine levels (IL-1β, IL-10, IL-13, IFN-γ, IL4, IL-5, IL-6, KC/GRO, TNF-α). Analysis of serum cytokines indicates that differential PAE responses to LPS or R848 occur mainly 90 min after injection. Male and female rats from both PAE and CON groups showed increased IL-10, IL-1β, IL-6, KC/GRO, and TNF-α levels 90 min following either LPS or R848 injection. However, PAE male and female rats showed higher IL-1β responses to R848 compared to CON, while only PAE male rats showed higher IL-6 and TNF-α responses to LPS and R848 relative to their CON counterparts. Moreover, both LPS and R848 increased IFN-γ levels in PAE but not CON females. Analysis of brain cytokines indicate that PAE also dysregulates central immune function in a sex dependent manner. Together, these data suggest that PAE results in hyperresponsivity to immune challenges and increased cytokine production, which play a critical role in the pathogenesis of autoimmune inflammatory diseases. Support: NIH/NIAAA R01 AA022460 and Azrieli Foundation to CR and TSB.

P3-C-639: Investigation of the impact of MYCBP2 loss of function on EPHB2 signaling, as a putative cause for neurodevelopmental defects

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Contact-mediated cell-to-cell communication is crucial for proper nervous system development and is often mediated by transmembrane receptors, such as EPHB2 receptor tyrosine kinase. EPHB2 regulates the repulsion of growing axons ensuring their precise targeting in developing neural circuits, as well as synapse formation and plasticity. Alterations in EPHB2 signaling have been linked with abnormal neuronal connectivity and synaptic dysfunctions causing learning disabilities, neuropsychiatric and neurodegenerative disorders. Nevertheless, a comprehensive model of how the deregulation of EPHB2 activities causes these pathological conditions remains to be elucidated. Detailed analysis of EPHB2 protein complexes via affinity purification-mass spectrometry revealed MYCBP2, an intracellular signaling hub in neurons, as a putative EPHB2 interactor. Recently, a cohort of patients with brain development abnormalities has been discovered to harbor mutations in MYCBP2. The fact that similar neurodevelopmental disorders are seen in patients with impaired EPHB2 signaling suggests that MYCBP2 and EPHB2 function in the same signaling pathway. Here, we explore the impact of MYCBP2 loss of function on EPHB2-evoked downstream signaling and cellular phenotypes. We evaluate how human mutations in MYCBP2 affect protein complex formation with EPHB2. We further generate MYCBP2 knockout mice utilizing CRISPR/Cas9 system to examine how MYCBP2 relays EPHB2 signals inside the neurons. Using this mouse model, we will perform experiments to address whether EPHB2-controlled neuronal connections are perturbed by mutations in MYCBP2. This study aims to reveal the disease mechanism of developmental disabilities caused by the altered function of MYCBP2-EPHB2 within the nervous system.

P3-C-640: Impact of kinin B1 receptor antagonism on visual function and choroidal neovascularization in a mouse model of age-related macular degeneration

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Objective: Loss of vision in age-related macular degeneration (AMD) results from choroidal neovascularization (CNV) infiltrating the retina, which is associated with inflammation. To prevent inflammation and CNV, we investigated the effect of a selective kinin B1 receptor (B1R) antagonist, R-954, a key element of pro- inflammatory kallikrein-kinin system, in a murine model of neovascular AMD. Methods: CNV was induced by laser burns in eight C57BL6 mice. 15µl eye drops of R-954 (100 µg) or saline was administrated twice daily for 7 days. Visual function was evaluated on days 0, 2, and 7 using electroretinography (ERG). CNV extent, cellular localization of B1R, and glial reactivity were evaluated using confocal microscopy. Results: Laser-induced CNV was accompanied by B1R staining in Müller cells, microglia proliferation, and disorganization of the vascular bed. 7-day topical treatment with R-954 maintained the choroidal and retinal integrity with significant decreases in CNV volume, B1R staining, and microglial invasion. Measurement of a and b-waves supported the maintenance of normal Müller

and photoreceptor cell activity by R-954. Conclusions: R-954 induced protection of retinal and choroidal integrity and function by inhibition of B1R-enhanced inflammation and neovascularization. Thus, this study provides strong pharmacological and anatomical evidence that non-invasive, self-administration of R-954 eye drops could be a promising therapy in AMD to preserve retinal health and vision.

P3-C-641: Phenomic characterization of orthologs of Parkinson's Disease-associated genes in C. elegans

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Current understanding of the genetic contributions of Parkinson's Disease (PD) has been expanded by advances made in genetic studies over the past decade, but efforts in the functional characterization of newly identified risk loci have become a bottleneck. To address this issue, we established a pipeline for the in vivo characterization of C. elegans orthologs of newly identified PD risk loci. C. elegans is ideal because: 1) C. elegans have orthologs to many PD-associated and biologically relevant genes. 2) We have access to a curation of strains harbouring loss-of-function mutations in almost every gene in the nematode genome. 3) Our lab developed the Multi-Worm Tracker for high-throughput characterization of behavioural and morphological phenotypes in populations of freely behaving animals in real time. Phenotyping strains with mutations in orthologs of PD-linked genes will yield novel phenotypic profiles for each disease-linked gene to inform follow-up investigations, and further analyses on the dataset may yield further insights on novel gene interactions or molecular pathways enriched in PD. A list of 180 mutant strains harbouring mutations genes orthologous to PD-linked genes, a majority of which are previously uncharacterized in disease relevance, will be phenotyped across an array of up to 30 behavioural and morphological features. This research will establish high-throughput genotype-to-phenotype characterization of newly identified risk genes for PD to inform future disease modelling efforts and further our understanding of the biological processes underlying PD.

P3-C-642: The effect of PD-linked VPS35 D620N mutation on endolysosomal homeostasis and trafficking

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We are interested in neuron-specific perturbations to endolysosomal homeostasis and trafficking IN THE CONTEXT OF of Parkinson's disease (PD). A mutation in VPS35 confers risk for late-onset, autosomal dominant PD, that is clinically indistinguishable from idiopathic PD. VPS35 encodes a subunit of the retromer complex, which reroutes lysosomal hydrolase receptors and synaptic proteins away from lysosomal degradation, back to surface membranes and other cellular compartments. The PD-linked D620N mutation impairs retromer's ability to orchestrate recycling, potentially leading to impaired endolysosomal clearance. Neurons are polarized, highly ramified, secretory cells, with intricate and electrochemically active neuritic networks. This places extreme demands on protein processing and traffic, which must service sites hundreds of microns from the cell body. Dopaminergic neurons in the

substantia nigra, which are vulnerable in PD, have especially high demands; they are tonically active pacemaker neurons which also exhibit high frequency burst firing, and their axonal arbors are the longest of any neuron. This may generally contribute to their vulnerability in PD, especially in the presence of mutations which perturb endolysosomal function. Here we explore the effects of VPS35 D620N mutation on endolysosomal homeostasis within neuronal somatic, dendritic, and axonal compartments. We compare neurons from VPS35 D620N knock-in mice with those of their wild-type littermates, and human VPS35-PD patient neurons against those from matched controls. We hope to establish a framework in which consideration of the spatial profile of endolysosomal organelles in neurons is essential to understanding endolysosomal dysfunction caused by D620N mutation.

P3-C-643: Lithium responsiveness in hyperexcitable neurons derived from bipolar patient iPSCs

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Bipolar disorder (BD) is a progressive psychiatric disorder characterized by recurrent mania and depression, often comorbid with psychosis and suicide. Paralleled with other treatments, the mood stabilizer lithium (Li) is the most effective medication to prevent manic and depressive episodes. However, the pathophysiology of bipolar disorder and lithium's mode of action is not yet fully characterized and understood. Some patients react well to Li treatment for undetermined reasons, while others are entirely non-responsive. Three major questions stand out i) how is Li effective, ii) why for only a subset of patients, and iii) could we find a treatment for the Li non-responders? Our previous studies showed that lithium dampens neuronal excitability and the activity of the glutamatergic network in mouse cortical neurons. Here, we have developed a human induced pluripotent stem cell (hiPSC) model for bipolar disorder and investigated the cellular phenotypes of glutamatergic cortical-like neurons derived from iPSCs of patients with bipolar disorder. Our results corroborate the literature discerning a hyperexcitability phenotype of young neurons, reversible by lithium in neurons derived from patients who clinically responded to lithium treatment. In this study, we combined cell imaging, electrophysiology, transcriptomic, phosphoproteomic, calcium imaging and pharmacological treatments to provide a molecular signature of disease, lithium responsiveness and alternative potential therapeutic candidates.

P3-C-644: SLP-2 decreases the susceptibility of dopaminergic neurons against alpha-synuclein toxicity in a mouse model of Parkinson's disease

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Accumulating literature has demonstrated a link between dysfunctional mitochondria and pathogenesis of Parkinson's disease (PD). SLP-2 is a scaffold protein that forms microdomains in the inner

mitochondrial membrane, which facilitates the assembly of respiratory chain complexes and their function. In PD brains, SLP-2 levels appear to be reduced in the midbrain dopamine (DA) neurons. Objective: We aimed to evaluate the neuroprotective role of SLP-2 in a preclinical model of PD. Methods: To study the role the neuroprotective role SLP-2 we performed gain and loss of function experiments in mice. We overexpressed (OE) SLP-2 by delivering an AAV vector encoding a Cre-dependant SLP-2 into the SNpc of DAT-Ires-Cre mice. To knock out SLP-2, we injected an AAV vector encoding two gRNAs against SLP-2 in DAT-Ires-Cre;Rosa26-LSL-Cas9 mice. Simultaneously, another AAV vector encoding the mutated A53T α-syn was co-injected to induce α-syn pathology and neurodegeneration. Four months post-injection, the mice were submitted to motor assessments. Then, DA axon density in the striatum and cell body in the midbrain were quantified. In parallel, we assessed mitochondrial functions in vivo and iPSC-derived DA neurons carrying α-syn mutations. Results: OE of SLP-2 in the nigral DA neurons prevented the apparition of motor deficits by protecting the DA striatal fibres and cell bodies in the SNpc. In contrast, KO of SLP-2 increases the susceptibility of DA neurons to α-syn toxicity. We also found that α-syn OE decreases mitochondrial oxygen consumption by altering mitochondrial morphology and membrane potential, which is restored by the SLP-2 forced expression. Conclusion: SLP-2 decreases the susceptibility of DA neurons against α-syn toxicity by rescuing mitochondrial functions.

P3-C-645: Ketamine differentially regulates cell-surface α5GABAA receptors in a time-dependent manner in mouse hippocampal neurons

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Introduction The mechanisms underlying the rapid antidepressant properties of ketamine remain poorly understood. One potential mechanism could be through the regulation of inhibitory transmission. In particular, increased activity of α5GABAA receptors (α5GABAARs) has been implicated in depression and negative allosteric modulators that selectively inhibit α5GABAARs have been shown to have rapid antidepressant effects similar to ketamine. Thus, we hypothesized that α5GABAARs may be involved in the antidepressant effects of ketamine. Specifically, we evaluate whether ketamine alters the cell-surface expression of α5GABAARs in hippocampal neurons. Methods Cultured hippocampal neurons were prepared from mouse embryos. Cultures were treated with ketamine (1μM or 10μM) for 1h or 24h. Surface α5GABAARs were labelled with biotin, then biotinylated proteins were precipitated with avidin agarose resin. Expression levels of surface α5GABAARs were detected and quantified by western blot. Results and conclusions A short, 1-hour treatment with ketamine resulted in a significant reduction in the expression levels of surface expression of α5GABAARs. In contrast, after the 24-hour treatment with ketamine, α5GABAARs were increased. These results suggest that ketamine differentially regulates cell-surface expression of α5GABAARs in a time-dependent manner, possibly through distinctive signalling pathways. These results identify a novel mechanism for ketamine's antidepressant properties and align with the growing evidence that the dose and duration of ketamine are crucial factors in the development of fast-acting antidepressants.

P3-C-646: Cell type-specific transcriptomic changes in human cortical microcircuits across psychiatric disorders

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Psychiatric disorders, such as major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ) are characterized by altered cognition and mood - brain functions that depend on information processing by cortical microcircuits. We hypothesize that psychiatric disorders manifest cell-specific vulnerabilities and transcriptional alterations in neuronal subpopulations that constitute cortical microcircuits; namely, glutamatergic pyramidal (PYR) neurons and vasoactive intestinal peptide- (VIP), somatostatin- (SST), and parvalbumin- (PV) expressing GABAergic interneurons. We performed cell type-specific molecular profiling, using laser capture microscopy and RNA sequencing in postmortem samples from subgenual anterior cingulate cortex (sgACC) in 19 tetrads (N = 76 total subjects) of control, MDD, BD, and SCZ subjects matched on age, sex, and tissue quality (University of Pittsburgh Brain Tissue Donation Program). Each cell type showed a unique profile of transcriptional changes that were shared in part across disorders, with interneurons showing greater transcriptomic changes than PYR-cells. Genes related to dendritic spine maintenance, immune activation, and protein metabolism were differentially dysregulated across cell types. Finally, we intersected our results with psychiatric GWASs to understand how disorder-associated variants may impact specific cell types. Overall, these results suggest deficits in cortical microcircuits in sgACC across psychiatric disorders, characterized primarily by changes in interneurons.

P3-C-647: Citrobacter rodentium infection in Pink1 WT and knockout mice leads to regional blood-brain-barrier dysfunction

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A growing body of research in the past decade supports the hypothesis that there are links between immune system activation and the development of Parkinson's disease (PD). In a recent study, we showed that repeated gastrointestinal infection with Citrobacter can lead to PD-like symptoms in Pink1 KO mice and immune cell entry in the brain. The objective of the current study was to test the hypothesis that such mild infections are sufficient to increase blood brain barrier (BBB) permeability and to cause brain inflammation . Pink1 WT and KO mice were infected with Citrobacter rodentium and at day 13 and 26 post infection, we conducted gadolinium-enhanced magnetic resonance imaging (MRI) to identify signs of BBB permeability. We also quantified expression of endothelial tight junction proteins and dopamine synthesis and transport proteins. Using MRI, we obtained support for the hypothesis that increased blood-brain barrier breakdown in both WT and Pink1 KO infected mice occurs 26 days after infection in the striatum, dentate gyrus, somatosensory cortex, and thalamus. This has been verified

using sensitive statistical methods applied to the T1 relaxation time probability distributions in each brain ROI . We found no change in expression of tight-junction proteins or DA markers in the striatum at both time points. However, preliminary data suggest chronic microglial and astrocyte activation at day 26 post infection. Our results support the hypothesis that even after mild gastro-intestinal infection, increased immune cell entry in the brain may occur, in part due to regional increases in BBB permeability. Our observations also suggest that this could cause increased microglial activation and thus promote that the establishment of a chronic state of brain inflammation.

P3-C-648: Long-lasting GABAA receptor overactivity in the hippocampus after surgery in mice

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BACKGROUND: Cognitive deficits occur frequently after surgery. Despite their prevalence and associated negative outcomes, the underlying causes are poorly understood. One potential mechanism is a sustained overactivity of extrasynaptic GABAA receptors. We previously showed that general anesthetic drugs trigger sustained overactivity of GABAA receptors, which manifests as increased inhibitory tonic currents and cognitive deficits. However, it remains uncertain whether excessive GABAA receptor activity is further increased after surgery. The goal of this study was to characterize GABAA receptor activity after anesthesia and surgery. METHODS: Adult C57BL/6 mice underwent abdominal surgery under isoflurane or sevoflurane anesthesia. Physiological parameters were monitored during surgery. Ex vivo brain slices were prepared 48-72 h later. The cell-surface expression and function of extrasynaptic GABAA receptors were studied using biotinylation assay and whole-cell voltage clamp recordings, respectively. RESULTS & CONCLUSIONS: Physiological parameters were stable during surgery. Cell-surface expression of extrasynaptic GABAA receptors increased following anesthesia and surgery. Ongoing electrophysiological studies will examine whether tonic inhibition is further increased. These results suggest that a sustained overactivity of GABAA receptors occurs postoperatively and GABAA receptors may be targeted to treat postoperative cognitive deficits.

P3-C-649: The effect of tau hyperphosphorylation on organelle transport

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Tau is a microtubule-associated protein that bundles and stabilizes microtubules in neuronal axons and regulates intracellular transport by kinesins and dyneins. We seek to understand how aberrant phosphorylation of tau alters intracellular transport and its contribution to the pathogenesis of Alzheimer's Disease and other tauopathies. Recently, we discovered that tau differentially regulates motility of specific cargoes based on the phosphorylation status of tau and the type of motors that carry them. Using TIRF microscopy, we examined how tau hyperphosphorylation leads to defective transport of lysosomes (lys) and early endosomes (EE) by exogenously expressing phosphomimetic tau (E14; mimicking tau hyperphosphorylation by GSK-3β kinase), phosphoresistive tau (AP14) and wild-type tau (WT) in COS-7 cells and tau-deficient iPSC-derived neurons. This model helps us dissect how defective

tau impacts intracellular transport. At neuronal expression levels, E14 tau in COS-7 localized primarily in the cytoplasm, in contrast to AP14 tau which enriched strongly on microtubules. All tau constructs reduced the processivity of EE and lys. AP14 tau inhibited the processivity and displacement of lys and EE more strongly compared to WT and E14 tau. AP14 acted as a strong barrier to the motors carrying cargo, due to its tight association with microtubules. Lys and EE motility was inhibited similarly by WT and E14 tau. Our preliminary results indicate that motors and tau compete for the binding sites on MT and that the E14 tau has weakened effects on cargo transport compared to AP14 tau.

P3-C-650: CD8+ T cell generated CD4+ T cells are important for the pathogenicity and infiltration of CD8+ T cells to CNS in an adoptive transfer EAE model.

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Both CD4+ and CD8+ T cells play critical roles in the immunopathogenesis of MS. 1C6 T cell receptor transgenic (TcR-Tg) mice on the NOD background have a MOG[35-55]-specific, MHC class II-restricted, TcR that selects for both CD4+ and CD8+ T cells. We recently demonstrated that in vitro differentiated 1C6 CD4 Th1 and Th17 cells can induce a progressive form of experimental autoimmune encephalomyelitis (EAE) upon adoptive transfer to NOD.Scid recipient mice. In this study, we assessed whether the same is true for 1C6 CD8+ T cells. 1C6 CD8 T cells differentiated and activated in response to plate bound anti-CD3/CD28 stimulus and also to the MOG35-55-antigen+APCs. Upon adoptive transfer 1C6 Tc1 and Tc17 cells (5x106 per recipient) induced progressive EAE. However, disease of increased severity and a higher number of CD8+ T cells was seen in the CNS upon co-transfer of Th1+Tc1 (2.5x106 of each per recipient). Intriguingly, ex vivo analysis of the spleens and CNS of Tc1-alone or Tc17-alone recipients revealed the presence of CD4+ T cells. This was observed even in mice receiving CD8+ T cells that were purified by high-speed cell sorting upon initial isolation from 1C6 mice; after in vitro culture but just prior to injection; and also at both time points. In vivo blockade of CD4 reduced not only the presence of CD4+ T cells in the CNS of Tc17 alone recipients but also the presence of CD8+ T cells; the frequency of splenic CD8+ T cells was either increased or not affected. This suggests that CD4/CD8 cooperation is required for the infiltration of the target organ by the latter. Together, our data indicate that the presence of both CD4+ and CD8+ T cells specific for the same CNS antigen is required for optimal CD8+ T cell pathogenicity in an adoptive transfer EAE model.

P3-C-651: Astrocytic α4GABAA receptors are critical for the anesthetic-induced persistent increase in tonic inhibition in hippocampal neurons

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BACKGROUND: Exposure to general anesthetic drugs including etomidate triggers a sustained increase in tonic current in neurons that is associated with cognitive deficits. Astrocytes are necessary for this effect,

as etomidate triggers a sustained increase in tonic current in astrocyte-neuron cocultures but not in neurons cultured alone. Anesthetic-sensitive GABAA receptors (GABAARs) are expressed in astrocytes, so we hypothesized that activation of GABAARs in astrocytes is necessary to trigger the sustained increase in tonic current in neurons. The first aim of this study was to identify the subtypes of GABAARs in astrocytes. The second aim was to knockout a major anesthetic-sensitive population of GABAARs on astrocytes and investigate whether this approach abolishes the etomidate-induced increase in tonic current in neurons. METHODS: Expression of GABAAR subunits in cultured astrocytes and neurons was profiled using ddPCR. For the major anesthetic-sensitive receptor subtype, knockout (KO) and wildtype (WT) cortical astrocytes were cocultured with CD1 hippocampal neurons. Cocultures were treated with etomidate for 1 h followed by complete media change which tonic current was measured using whole-cell patch clamp 24 h later. RESULTS: We found that astrocytes predominantly expressed α4 and α2, as well as β1, β3 and γ3 subunits. We created cocultures using α4KO astrocytes, since α2KO mice are non-viable. Etomidate increased tonic current in neurons cocultured with α4WT astrocytes but not in neurons cocultured with α4KO astrocytes. CONCLUSION: These results suggest that α4GABAARs in astrocytes are necessary for the etomidate-induced increase in tonic current in neurons. These receptors may represent a novel targeted to mitigate cognitive deficits after general anesthesia.

P3-C-652: Elucidation of IL-1 receptor-mediated mechanisms in inflammation and pain responses

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INTRODUCTION In individuals with inflammatory autoimmune diseases, chronic pain is present in more than 50% of patients. Pain is transmitted by nociceptors to the spinal cord and the brain via dorsal root ganglions (DRGs). The interleukin (IL)-1β can trigger both inflammatory and pain responses. OBJECTIVE Identify the mechanisms mediating the inflammatory and pain responses induced by IL-1β. METHODS Injections of recombinant mouse IL-1β were performed in mice globally lacking the type 1 IL-1 receptor (IL-1R1), mice with a cell-specific deletion or restoration of the Il1r1 gene, and their respective control mice. We then carried out quantifications of the types of neurons expressing IL-1R1. We also performed various behavioral tests. Finally, we performed 5'RACE-PCR on total RNA isolated from DRGs. RESULTS IL-1R1 is expressed exclusively in a nociceptor subtype that expresses TRPV1. Deletion of Il1r1 specifically in these nociceptors prevented the development of mechanical pain in mice with experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, without affecting other clinical signs of the disease. Moreover, restoring Il1r1 expression exclusively in these nociceptors in otherwise IL-1R1 knockout mice resulted in full restoration of pain behaviors in EAE. We also detected from total RNA extracted from DRGs the presence of transcription start sites within the Il1r1 gene which would be distinct and potentially correspond to τIL1R1, as described by Qian et al. CONCLUSION IL-1β may trigger inflammation and pain through different receptors and signaling pathways. Notably, TRPV1+ nociceptors may express a truncated form of IL-1R1, τIL1R1, causing the pain response.

P3-C-653: A novel peptide to prevent excessive cell-surface expression of α5GABAA receptors in mouse hippocampal neurons

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Introduction: Excessive α5GABAA receptor (α5GABAAR) activity is associated with a variety of cognitive, developmental and mood disorders. Currently, there are limited strategies to treat or prevent these disorders. Cell-surface expression of α5GABAARs is regulated by radixin, a cytosolic protein that anchors α5GABAARs. Disrupting the interaction between radixin and α5GABAARs may reduce cell-surface expression. Our lab designed a peptide (US patent 10,981,954) that mimics the binding site of radixin on α5GABAARs to disrupt this interaction. Methods: Cultured hippocampal neurons were prepared from embryonic mice and cultured for 13-15 days. Neurons were treated with ifenprodil, an NMDA receptor antagonist that increases cell-surface expression of α5GABAARs, or vehicle for 24 h. A subset of neurons were cotreated with ifenprodil and TAT-peptide or TAT-scrambled peptide for 24 h. Cell-surface expression of α5GABAARs was assessed using multicolor immunofluorescent staining and biotinylation assays. Results and Conclusions: Ifenprodil increased cell-surface expression of α5GABAARs identified by both immunofluorescence and biotinylation assays. Ongoing experiments will determine whether the peptide will prevent the increase in cell-surface expression. We anticipate that our results will elucidate a promising novel strategy to treat disorders associated with excessive α5GABAAR activity.

P3-C-654: Altered microRNA expression in extracellular vesicles from degenerating human neurons

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The development of neurodegenerative diseases often begins long before symptom onset, highlighting the importance of early disease detection and diagnosis. Extracellular vesicles (EVs) - small vesicular bodies secreted by cells - are promising sources of biomarkers for central nervous system diseases. EVs can cross the blood-brain barrier, are found in abundance in peripheral biofluids and enclose molecular cargo that reflect their cell of origin. Among their cargo are microRNAs: non-coding RNA molecules that regulate gene expression in healthy and pathological conditions. Recent studies have identified dysregulated microRNA expression in EVs from patients with neurodegenerative diseases; however, the source of these microRNAs is unknown, providing little information about underlying disease biology. Here, we use a reductionist in vitro culture system to profile microRNA expression in EVs secreted by degenerating neurons. Human induced pluripotent stem cells (iPSCs) were differentiated into mature cortical neurons and challenged with toxic stimuli to induce degeneration. EVs were isolated from the cell culture media of degenerating neurons and subjected to microRNA-sequencing. We identify a panel of microRNAs that are dysregulated in EVs from degenerating neurons. These microRNAs can be analyzed in EVs from patients with neurodegenerative diseases to establish diagnostic or prognostic biomarkers of neuronal damage.

P3-C-655: Investigating the role of a novel TDP-43 modification in protein mislocalization and ALS

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TDP-43 (tar DNA-binding protein 43) is an important gene that leads to both sporadic and familial forms of ALS (amyotrophic lateral sclerosis). Although the presence of TDP-43-containing cytosolic inclusions is the hallmark of ALS, the underlying cellular processes are not well understood. Since it is hypothesized that TDP-43 pathology arises from its cytoplasmic mislocalization, we investigated whether this may be mediated by palmitoylation, a modification with important roles in protein trafficking and membrane-related processes. Palmitoylation involves the covalent addition of palmitate to cysteines, and has been predicted for TDP-43. However, this has not been confirmed. Using biochemical assays of palmitoylation, we are the first to experimentally confirm TDP-43 palmitoylation using alkynyl palmitate labeling and click chemistry detection in mammalian cell culture. In addition, we observed exacerbated TDP-43 nuclear loss and increased cytoplasmic mislocalization when treated with the cell stressor sodium arsenite in combination with the de-palmitoylation inhibitor, as opposed to treatment with sodium arsenite alone, suggesting that increased palmitoylation may be involved to TDP-43 trafficking and mislocalization. Further, our data suggests that palmitoylation may compete with and precede nitrosylation, another cysteine modification previously shown to contribute to TDP-43 mislocalization and aggregation. Our findings provide foundational insight on a novel pathway to further our studies of protein mislocalization and aggregation in neurodegenerative diseases.

P3-D-656: β-Arrestin recruitment and biased agonism at the M1 muscarinic receptor

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We recently showed that application of selective (pirenzepine (PZ)) or specific (muscarinic toxin 7 (MT7)) antagonists of muscarinic acetylcholine type 1 receptor (M1R) prevent or reverse nerve degeneration in different rodent models of peripheral neuropathy. In vitro studies have revealed that β-arrestin (βArr) signaling played a role in mediating these effects. To understand the mechanism of action of PZ and MT7, we investigated whether these drugs possess βArr-biased agonism at M1R. Results from a proximity assay in HEK293 cells showed M1R agonists and antagonists recruit β-arrestin2 to M1R in a time-dependent manner. Unlike MT7 and PZ, muscarine increased inositol-phosphate 1 (a marker of Gαq activation) levels in both HEK293 and dorsal root ganglia (DRG) neurons. Also, MT7 and PZ increased ERK phosphorylation in M1R-expressing HEK293 and DRG neurons in a time-dependent manner. These results suggest PZ/MT7 possess βArr-biased agonism. Role of Gαq-protein and βArr in PZ/MT7-induced ERK activation was investigated using a specific Gαq inhibitor and βArr KO HEK293 cells, respectively. Results showed, unlike Gαq protein, βArr are necessary for PZ/MT7-induced ERK phosphorylation. Using phospho-specific immunoblotting, PZ/MT7 impacted serine/threonine phosphorylation status of M1R. Internalization assay results showed PZ/MT7 not only did not induce M1R internalization but increased surface expression of the receptor. Overall, this study provides molecular evidence to support a role for selective/specific muscarinic receptor antagonists acting as biased agonists at the M1R.

P3-D-657: Uncovering the mechanism for motion computation in Drosophila melanogaster

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Diverse sensory systems, from audition to thermosensation, feature a separation of inputs into ON (increments) and OFF (decrements) signals. In the Drosophila visual system, separate ON and OFF pathways compute the direction of motion. Our previous work used in vivo whole-cell recordings to show that directional selectivity in both the ON and the OFF pathways originates from simple integration of spatially offset fast excitatory and slow inhibitory inputs. We constructed a passive, conductance-based model using only responses to flashing stimuli and showed that the model can accurately predict ON and OFF neuronal responses to complex moving stimuli. Here, we used this well-studied circuit to ask whether the motion computation depends on ON-OFF pathway crosstalk. We recorded visual responses of ON and OFF cells, mapped their composite receptive fields, and found that they share a similar spatiotemporal structure. We have updated our model and found it provides a mechanistic explanation for the directional preference inversion in response to a prominent visual illusion. We validated the model's predictions using behavioral measurements in tethered flying flies. Finally, we used the whole-brain Drosophila connectome to investigate how ON-OFF motion information is integrated by downstream neurons.

P3-D-658: Investigating the role of the lateral substantia nigra pars compacta in modulating voluntary movement

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Dopaminergic neurons (DAs) of the substantia nigra (SN) play a critical role in voluntary movement. This is evident as Parkinson's disease renders individuals with motor deficits. However, despite decades of research, their mechanistic role in modulating movement remains unclear. This could be in part due to the heterogeneous nature of SN DAs not being accounted for in behaviour studies. Recent work suggests that phasic DA activity prior to movement promotes its initiation and vigour. However, these studies typically report locomotion as the only measure of voluntary movement, and measure movement over a limited time range. The aim of this study was to address two knowledge gaps: whether lateral SN DA activity promotes voluntary movement, and whether other voluntary behaviours, including locomotion and exploratory behaviour, are impacted. To probe these questions we used optogenetic stimulation of a transgenic mouse model expressing channelrhodopsin in DAs. Our results suggest that stimulation of lateral SN DAs causes voluntary movement, both locomotion and other forms of exploration, such as rearing, over multiple recording trials. In addition, similar to other labs' findings over smaller time frames, the effect of a stimulation trial may promote movement in subsequent consecutive trials. These findings suggest that lateral SN DA activity not only permits wanted movements, but plays an active role in promoting them during ongoing activity. Furthermore, our study adds insight into the time frames over which DA activity impacts movement and exploratory behaviour.

P3-D-659: Functional contribution of midbrain nuclei to locomotor recovery after spinal cord injury

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Electrical stimulation of the midbrain has been shown to improve locomotor recovery after spinal cord injury (SCI). Are part of this functional region: the cuneiform nucleus (CnF) and the pedunculopontine nucleus (PPN). We have recently shown that activation of glutamatergic CnF neurons initiates and accelerates locomotion, whereas glutamatergic and cholinergic PPN neurons decelerate and stop locomotion in the mouse. We hypothesized that these distinct neuronal populations contribute differently to locomotor recovery after SCI. Transgenic VGluT2-cre mice were injected with AAV to genetically ablate or photostimulate glutamatergic CnF or PPN neurons. Although mice dragged initially their ipsilesional hindlimb, they recovered locomotor functions by the 3rd week post-SCI. 7 weeks post-SCI, genetic ablation of VGluT2+CnF neurons deteriorated motor functions during walking and swimming, whereas ablation of VGlut2+PPN neurons mildly impaired swimming. Short photostimulations of VGluT2+CnF or PPN neurons evoked phase-dependent electromyographic (EMGs) responses in hindlimb muscles during locomotion. Responses decreased at week 1 post-SCI but recovered by week 4 with locomotor recovery. Furthermore, long trains of photostimulations of VGlut2+CnF neurons improved and accelerated the locomotor pattern and rhythm, whereas VGlut2+PPN neurons failed to improve locomotor functions. Although the PPN has been considered as a target in clinical settings, our study argues that glutamatergic neurons of the CnF will be a better neurological target to improve functional locomotor recovery in SCI patients.

P3-D-660: Repetitive transcranial magnetic stimulation induces cortical layer and brain region specific gene expression changes

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Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive tool commonly used to study neural plasticity and treat neurological disorders. Despite its popularity, the cellular mechanisms underlying rTMS-induced plasticity and how this varies between different neural circuits is poorly understood. We aimed to characterise the genes and biological pathways affected by rTMS and identify how this varies between brain regions using a mouse model. Bulk RNA-sequencing was used to determine differences in neural plasticity mechanisms recruited in the motor cortex between two established rTMS protocols (continuous and intermittent theta burst stimulation - cTBS and iTBS). Spatial transcriptomics was used to map changes in plasticity across cortical layers and brain regions following iTBS targeted to the motor cortex. Relative to sham, only cTBS led to gross changes in gene expression of the motor cortex. In our spatial transcriptomics experiments, iTBS induced plasticity across all 6 cortical layers which differed between the motor and sensory cortices. Surprisingly, the greatest changes to gene expression occurred in subcortical regions and not in cortical regions. Our findings demonstrate that cTBS but not iTBS leads to gross gene expression changes in the motor cortex. In addition, we demonstrate that rTMS induced changes to gene expression are cortical layer and brain region specific. These results highlight the

complexity of rTMS-induced plasticity across the brain and the need to consider the effect of rTMS on local and distant circuits prior to its use.

P3-D-661: Impact of exercise on neuropathic pain and spinal microglia

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Introduction/Aim: Disease or damage to the peripheral nerves can produce neuropathic pain, one of the most debilitating chronic pain conditions. Recent pre-clinical and clinical studies suggest that exercise reduces pain and improves motor recovery following nerve injury, but how this occurs is unclear. We test the hypothesis that exercise augments microglia function, immune cells that reside in the central nervous system, which alters pain responses. Methods: Spared nerve injury surgery was performed on male and female C57BL6/J and CX3CR1creER; Rosa26tdTom mice. With an appropriate interval following tamoxifen induction, these mice enabled fate-mapped microglia to be delineated from monocyte-derived macrophages. Animals were trained on an in-house designed voluntary running wheel with an Arduino-powered base. Each animal was tagged with a unique radio-frequency identification tag to track running distances, duration, and speed. Allodynia following nerve injury was measured using von Frey filaments. Immunohistochemical changes in the lumbar spinal cord dorsal and ventral horns, both ipsilateral and contralateral to the injury, were analyzed to assess the effect of exercise on spinal circuitry and microglial profile. Results: Exercise before and after nerve injury impacts nerve injury-induced changes in sensory nerve innervation and motor circuitry in addition to reducing mechanical hypersensitivity. Discussion/Conclusions: We demonstrate that exercise modulates spinal microglia reactivity and synaptic connectivity critical for sensory processing. Elucidating specific cellular targets engaged by exercise presents novel therapeutic treatment opportunities for neuropathic pain.

P3-D-662: Sensing the Environment: Using Olfaction to Understand Dietary Preferences in Lake Sturgeon Acipenser fulvescens

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Olfaction contributes significantly to the ability of the Lake Sturgeon Acipenser fulvescens to sense its environment and is a crucial mechanism for feeding. The olfactory epithelium contains three olfactory sensory neurons (OSNs)--ciliated, microvillous, and crypt cells--that detect unique compounds such as amino acids, bile salts, and pheromones. We first used electrophysiological and behavioural techniques to evaluate diet cue detection and potential transduction pathways of olfaction in one-year-old Lake Sturgeon to the current hatchery and wild-type diet cues. The amplitude of the electro-olfactogram (EOG) response did not correlate to increased foraging activity in a behavioural arena, although behavioural responses for the hatchery cue were significantly greater compared to the wild-type. Further, EOG responses to complex dietary cues required activation from both ciliated and microvillous

OSNs with responses decreasing significantly when inhibitors Forskolin or U-73122 was applied. We then investigated if acute treatment with L-alanine during the early life stage influenced olfactory development and survival. We used molecular, electrophysiological, and behavioural techniques to assess these effects. The treatment significantly affected mRNA transcript abundance of olfactory genes V2R1-like, V2R26-like, OR1-like and TAAR1-like throughout development as well increased activity levels in age-0 Lake Sturgeon. These findings suggest that environmental olfactory cues may play a role in early development, possibly creating low-performance phenotypes in hatchery settings.

P3-D-663: Mapping dopamine receptor subtypes in the human brain

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Dopamine (DA) plays key roles in motor, emotional and cognitive functions. The outcome of DA signals and effectiveness of dopaminergic drugs rely on the relative preponderance of each of the 5 DA receptors within the brain. The contribution of each receptor subtype to overall dopaminergic tone is difficult to establish at a functional level due to a lack of subtype specific pharmacological agents. A surrogate for receptor function is its protein or mRNA level. Hence, understanding the relative abundance of each receptor and their combinations is essential for envisaging the overall impact of DA signals in normal and disease states. To date, several studies have investigated the distribution of DA receptors in human brain, using autoradiography and in situ hybridization. However, these studies share the limitation of focusing on a single receptor, mostly D1 or D2 and occasionally D3, while co-expression studies are lacking. Specifically, all 5 DA receptors have never been studied together. In the present endeavor, using multiplexed fluorescent in situ hybridization, we profile individual distributions as well as co-expression patterns of the entire DA receptors repertoire in various regions within healthy control human brains. Fresh-frozen brain structures were obtained from the Douglas-Bell Canada Brain Bank. Moreover, we interrogate the cell specific nature of these expressions using validated markers selective for different brain cell types. Our findings so far from caudate, putamen and nucleus accumbens reveal a great level of heterogeneity across different brain regions.

P3-D-664: Optimal time-window to apply cortical stimulation for maximal recovery of walking after spinal cord injury

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Incomplete spinal cord injuries (SCI) are associated with chronic motor deficits. The ability to walk is often lost after SCI, reducing independence and quality of life. A long-standing question in the field of rehabilitation is: when should we start therapeutic interventions for optimal neurological outcomes? To address this question, we developed the first neurostimulation strategy that directly targets the motor cortex during ongoing locomotion (Bonizzato and Martinez, 2021). To evaluate the effectiveness of this stimulation strategy, we used a rat model of incomplete SCI (unilateral hemisection at T8). Cortical stimulation was applied 30 min/day for three weeks during treadmill training, starting at one (acute

group, n=3), four (subacute group, n=3) or eight weeks (chronic group, n=1) after incomplete SCI. Locomotion recovery was assessed for 15 weeks on a treadmill and horizontal ladder. Our preliminary results showed an immediate improvement in locomotor performance (reduction in foot-dragging and the number of faults in the horizontal ladder) from the first week of therapy in all three groups. More importantly, performance for the acute and subacute groups was maintained for one month after treatment discontinuation. These preliminary data suggest that our therapeutic intervention is effective even when initiated in the early phase after SCI, an encouraging result considering that neurorehabilitation is generally started late in the clinic. Reference 1- Bonizzato M and Martinez M. An intracortical neuroprosthesis immediately alleviates walking deficits and improves recovery of leg control after spinal cord injury. Science Translational Medicine 2021, 13(586):eabb4422

P3-D-665: Encoding of vibrotactile stimuli by mechanoreceptors in rodent glabrous skin

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Our understanding of somatosensory processing in rodents comes primarily from the whisker system whereas the coding properties of low-threshold mechanoreceptors (LTMRs) in rodent glabrous skin have yet to be well characterized. An LTMR's response to touch is influenced by stimulus intensity (rate coding) and frequency (temporal coding). Rate and temporal coding are influenced by the probability of a spike occurring on each cycle (i.e. spike reliability) and the timing of spikes relative to the stimulus cycle (i.e. spike precision), respectively. Accordingly, through in vivo extracellular recordings in rodents, we measured the reliability and precision of LTMR responses to sinusoidal vibrotactile stimuli between 2 and 300 Hz. LTMRs were first classified as rapid adapting (RA) or slow adapting (SA) based on their response to sustained pressure. Heterogeneity in the response of RAs to vibration revealed a spectrum of frequency preferences across this LTMR subtype. Furthermore, although stimulus frequency differentially affected spike reliability across different RAs, increasing frequency universally increased spike precision. Finally, to explore the mechanisms supporting the unique tuning properties of rodent LTMRs, we fit generalized linear models to experimental data. Our models reproduced experimental reliability and precision and demonstrated that the integration time window of different RAs transitions from wide to narrow as tuning preference across the population moves from low to high frequencies. Together, these experimental results strengthen our understanding of somatosensory processing in rodents, and the resulting models allow us to efficiently dissect the coding properties of different LTMR subtypes.

P3-D-666: Challenges to the development of large-scale tele-audiological interventions for the elderly population

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In Canada, more than 64% of adults aged between 60-79 have hearing loss. Pure tone thresholds can be used to detect age-related hearing loss, also known as presbyacusis. Among elders more than 70% are

unaware of their hearing problem. The association between unaided prebyacusis, cognitive decline and dementia has gained international recognition among medical organizations and scientists. These statistics point to an increasing demand for audiological services among the elderly. Secluded living conditions, reduced mobility and other health problems are thought to affect elderly adults' access to audiological care. To address this lack of access to audiological services, tele-audiology becomes an interesting avenue. However, to be able to develop large-scale tele-audiological interventions for the elderly, several parameters needs to be addressed. While some attempts have been made to use tele-audiology in older adults, this kind of interventions has not been systematically explored, and the related challenges to their deployment have not yet been systematically mapped. First, we aimed at clarifying what is the definition of an elder in the audiology field. Secondly, we wanted to address the current literature's challenge of interoperability, which is a barrier to the generalisation of interventions and recommendations. Finally, we were able to identify the social-technical implications of these services and make some practical recommendations for clinicians as a result of this scope review.

P3-D-667: Investigation of differentially expressed genes between spinal cords of adult male and female mice

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Chronic pain is a highly debilitating condition that differs by type, prevalence and severity between men and women. To uncover the molecular underpinnings of these differences, it is critical to analyze the transcriptomic composition of heterogenous cell types found within in the spinal cord pain processing network. Despite several recently published single-cell RNA sequencing (scRNA-seq) studies on the mouse spinal cord, a sex-stratified analysis has yet to be performed. Here, we combined data from three different large-scale scRNA-seq studies which used sex-identified adult mice (Alkaslasi et al., 2021, Nat. Commun., Blum et al., 2021, Nat. Neurosci., Sathyamurthy et al., 2018, Cell Reports). Using the Seurat framework, we clustered and classified more than 43,000 unique cells, and then utilized DESeq2 to list differentially expressed genes between males and females. We categorized differences in gene expression by cell type, enabling investigations into difference that are specific to neurons, astrocytes, microglia, and other spinal cord cell types. We have therefore identified specific genetic players within the rodent spinal cord that diverge between males and females, which may underlie reported sex differences in spinal nociceptive mechanisms and pain processing. This work also provides insights into important physiological spinal mechanisms of sensory and motor function as well as a framework for future sex-stratified scRNA-seq analysis of human spinal cord tissue.

P3-D-668: Uncovering the role of Podxl in photoreceptor cell function and survival

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Light detection by rod and cone photoreceptors in the mammalian retina relies on the precise compartmentalization of their apical domain into an outer and inner segment. While critical for photoreceptor function and survival, it remains unclear how this polarity is established and maintained. In this perspective, Podocalyxin-like protein (Podxl) poses as an interesting candidate. First identified in the kidney where it acts to regulate protein localization and epithelial cell polarization, Podxl has recently been discovered to locate at the membrane of cone inner segments, and our recent results indicate that Podxl is also found in rod inner segments. To elucidate Podxl function in photoreceptors, we conditionally inactivated Podxl in rods and cones using the Cre-loxP system. We found that loss of Podxl in cones significantly impacts light-mediated response in the retina. To elucidate how Podxl mediates this effect, we used IP-MS to identify potential interacting partners. The top interactor, PDZ and Plekstrin Homology domain protein 1 (Pdzph1), is hypothesized to be involved in the polarized trafficking of cargos important for vision from the inner to outer segments. Preliminary results indicate that Pdzph1 localizes to the inner segment, and interacts with Podxl. Future work is aimed at further investigating this interaction and how it affects photoreceptor biology and phototransduction. As Podxl function has never been examined in the retina, this project will lead to a better understanding of retinal diseases in which photoreceptor polarity is compromised.

P3-D-669: Serotonergic neurons in the dorsal raphe encode attentional signals during visually guided behavior

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Visual perception arises when internal states of the brain focus our visual system on the most behaviorally salient stimuli. The neuromodulator serotonin (5HT) is among the most important carriers of such state information, but little is known about how its release in visual areas impacts the processing of visually guided behavior. Here we show that 5HT release by the dorsal raphe (DR) regulates visual attention and detection in the awake and behaving mice. We trained mice to perform a visually guided detection task in which mice searched for a 3-bar grating pattern embedded in dynamic checkerboard noise, and simultaneously collected fiber photometry recordings of DR neural activity. Doing so revealed that DR activity decreased when animals attended to a screen to detect the grating stimulus. By employing a genetically encoded sensor of 5HT release, we found that this decrease in DR activity corresponded to a drop in 5HT release in mouse visual cortex. By using optogenetic actuators to elevate or suppress DR neural activity while mice perform our tasks, we demonstrated that suppression of DR activity enhanced visual attention and detection, whereas elevation of DR activity suppressed visual attention and detection. Based on this, we conclude that DR 5HT release comprises a novel attentional signal that regulates detection of salient visual stimuli. These results provide a new framework to understand 5HT neuromodulation in visually guided behavior and provide an entry point to study diseases (eg. autism spectrum disorder) in which 5HT signaling and visual perception are disrupted.

P3-D-670: Sensory predictions are embedded in cortical motor activity

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When moving through the world, such as biking down a bumpy trail, we encounter external forces that cannot be predicted by our own motor output. Since delayed sensory feedback is too slow to allow accurate state estimation, predicting expected sensory input could make rapid feedback control more stable. However, we don't know how flexibly the nervous system can use prior information to make sensory predictions, nor how these predictions are implemented in the brain. To answer this, humans and macaques performed a reaching task where visual cues indicated the probability of the direction of upcoming elbow perturbations. Humans and monkeys integrated these priors into sensory predictions on single trials, biasing their responses, as measured by muscle activity, within 70 ms of perturbation onset, faster than the time it takes to initiate a 'voluntary' movement. High-density neural recordings in monkeys revealed a widespread signature of sensory predictions in prefrontal, premotor, and motor cortex, but not in somatosensory cortex. An artificial neural network trained to perform reaching tasks by controlling a biomechanical model of the arm naturally learned to make sensory predictions, showing remarkably similar muscle and neural activity to humans and monkeys. Together, these results uncover a link between sensory predictions and movement - neural dimensions responsible for detecting perturbations are biased by sensory predictions before movement, allowing the brain to rapidly act when a perturbation is detected, but before details about the perturbation are fully resolved.

P3-D-671: Cerebellar nuclear neurons receive non-random Purkinje cell input

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The connections between neurons form the foundations of brain circuits, and their spatial properties influence circuit function. In the cerebellum, Purkinje cells integrate extensive synaptic input and transmit this information to cerebellar nuclear neurons, the output cells of the cerebellum. The connections between Purkinje cells and cerebellar nuclear neurons represent a crucial component of the cerebellar circuit, but how Purkinje cells spatially converge onto nuclear neurons is poorly understood. To explore Purkinje cell-nuclear neuron connectivity, we performed whole-cell recordings from nuclear neurons in acute slices, using optogenetics to focally stimulate Purkinje cell axons at multiple locations. We recorded evoked postsynaptic currents from nuclear neurons and produced spatial connectivity maps. Purkinje cell input clustered into the four cerebellar transverse zones and exhibited non-random connectivity with nuclear neurons. Some nuclear neurons received input from Purkinje cells located within a single zone, while others received input from multiple zones. Surprisingly, a subset of nuclear neurons received input from all four zones: this four-zone connectivity motif occurred more often than predicted by a random model. Next, we performed viral labeling of Purkinje cells across multiple zones and saw that Purkinje cell convergence patterns are morphologically similar to our functional data. Lastly, in paired cell-attached and whole-cell recording experiments, we found that small inputs are sufficient to pause nuclear neuron activity, thus affecting cerebellar output. Our findings highlight that

non-random motifs underlie cerebellar cortical output, and that cerebellar nuclear neurons may function as a novel locus of integration within the cerebellum.

P3-D-672: A vocalization-processing network in marmosets

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Vocalizations play an important role in the daily life of primates and likely form the basis of human language. fMRI studies have shown that listening to language or reading activates a left-lateralized fronto-temporal language network in humans. A similar network has been identified in macaques using fMRI and single neuron recordings. Here, we investigated whether New World common marmosets (Callithrix jacchus) also possess a conspecific vocalization-processing network. We presented conspecific vocalizations, scrambled vocalizations, and nonvocal complex sounds to five adult awake marmosets through a block design paradigm in a passive auditory task during sparse-sampling fMRI acquisition at ultrahigh field (9.4T) while subjects were immobilized using a house-built head-fixation system. To investigate the functional and structural connectivity of vocalization processing areas, we compared our results with resting-state fMRI and tracer-based maps. Finally, for a qualitative comparison of the identified areas with the human language network, we used a probabilistic atlas for the human language network. Our results demonstrate a vocalization processing network in marmosets that includes auditory, frontal, and cingulate cortices as well as subcortical areas. The findings suggest that the human language network has evolved from an ancestral vocalization network that predates the separation of New and Old World primates. These results provide a foundation for further invasive explorations of this network in marmosets and support this species as a valuable model for vocal be

P3-D-673: Retinal ganglion cell types contribute to distinct aspects of visually guided prey capture

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The visual scene is decomposed by retinal circuits into several representations that each contain emphasis on a specific feature such as motion. Each feature representation is sent to the brain along the axons of a specific retinal ganglion cell (RGC) type, but little is known about how individual representations contribute to innate behavior. To address these issues, we trained mice to perform a visually guided prey capture assay and compared their performance after silencing specific RGC types. We segmented predation behavior into 6 syllables called approach, pursuit, contact, miss, explore, and freeze. By examining the spatiotemporal structure of these syllables, inter-syllabic transitions, and prey position we show that hunting is a stereotyped sequence of syllables evoked by specific arrangements of mouse and prey. By comparing these syllable sequences to those obtained in mice with chemogenetically perturbed direction-selective and αRGCs, we discovered two distinct type-specific contributions to syllable structure and progression. Taken together, these data show that feature encoding in RGCs contribute to distinct aspects of visually guided prey capture.

P3-D-674: Altered input/output properties of layer 5 pyramidal neurons in vivo in a mouse model of Fragile X syndrome

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Interacting with our environment requires our brain to combine sensory information with our internal representation of the world. Cortical layer 5 (L5) pyramidal neurons (PN) are believed to play an important role in this process since these neurons receive predictive and sensory inputs at their apical and basal dendrites, respectively. Changes to the integration of excitatory inputs in cortical neurons likely contributes to the behavioral phenotype associated with neurodevelopmental disorders such as Fragile X syndrome (FXS). FXS is the most frequent form of inherited intellectual disability and common known cause of autism. We have recently shown that while subthreshold excitatory inputs integrate linearly in the basal dendrites of L5 PN of control animals, surprisingly those of FXS summate sublinearly, contradicting what would be expected of sensory hypersensitivity classically associated with autism spectrum disorders. We tested how this altered synaptic integration impacts how the brain encodes sensory information (whisker puff) using in vivo calcium imaging and extracellular recording techniques. In both sets of experiments, we found that FXS L5 PN exhibited less stimuli-driven responses and more non-stimuli-driven activity. These results support our hypothesis that FXS is characterized by more than just a global cortical hypersensitivity, but rather a hyposensitivity of sensory inputs and hypersensitivity of predictive inputs onto cortical neurons. This work is funded by the CIHR, as well as FRQS and QART postdoctoral fellowships to DEM.

P3-D-675: Biased opioid-neurotensin chimeric compounds for pain management

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The clinical management of various types of pain relies on the use of opioid analgesics. Paradoxically, long-term use and increasing doses of opioids are accompanied by diverse adverse effects, witch are primarily mediated by mu-opioid receptor (MOR) activation, including constipation and respiratory depression. In the search for safer analgesics, G-protein versus β-arrestin biased agonism at the MOR has been proposed as an opportunity to produce antinociception with reduced adverse effects. Futhermore, the design of multifonctional ligands co-targeting opioid and non-opioid receptors offers a promising strategy for the treatment of pain. As one of the non-opioid pharmacophores, neurotensin (NT) receptor agonists can be considered in the rational design of such chimeric compounds. These new opioid-NT hybrids were characterized in vitro for their affinity and selectivity towards MOR, DOR, NTS1 and NTS2 receptors. All opioid-NT hybrid peptides exhibited high affinity for NTS2 (1 to 5 nM), good selectivity over NTS1 (Ki>1800 nM), and MOR affinity values in the subnanomolar range (<1 nM). In addition, the replacement of βAla by Gly or GABA slightly improved DOR binding. BRET-based biosensors were then used to measure the potency and efficacy of the bifunctional peptides in MOR and DOR β-arrestin-2 recruitment and Gαi activation. Interestingly, these chemical modifications result in chimeric peptides

with either partial agonist activity or biased signaling profiles at the opioid receptors. Finally, their analgesic efficacy, assessed using the rat acute tail-flick pain model, revealed a strong analgesic effect after intrathecal administration. Hence, these opioid-NT hybrids represent a promising avenue towards the development of safer analgesics.

P3-D-676: NeuroCSF: a novel fMRI method to measure human contrast sensitivity function

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The contrast sensitivity function (CSF) describes a range of spatial frequencies (SF) that are detectable at a given level of contrast, and is a very valuable tool both in clinical and fundamental research. However despite its immense value, the full potential of the CSF has not been utilized in every aspect of clinical research due to time limits and patient factors. We propose neuroCSF as a new method for measuring the CSF across the visual field directly from brain activity, and with minimal demand from participants. NeuroCSF is a computational model that estimates voxel-wise CSF parameters from functional magnetic resonance imaging (fMRI) signals, under controlled visual stimulation conditions. The approach extends the population spatial frequency tuning (Aghajari, Vinke, & Ling, 2020) and population receptive field (Dumoulin & Wandell, 2008) methods, and provides the first complete characterization of a full CSF using neuroimaging data. We derived robust estimates of cortical CSF and show how CSF parameters vary across locations in the visual cortex. We observe that across early visual areas (V1, V2 and V3), the CSF peak SF is significantly higher for foveal eccentricity and decreases at parafoveal eccentricities. Conversely, V1 SF bandwidth slowly increases with eccentricity, while peak contrast sensitivity remains constant with eccentricity for all early visual areas. Thus, cortical CSF estimates vary systematically with eccentricity. The new neuroCSF approach enables objective and reliable estimates of cortical CSF parameters using fMRI neuroimaging. The procedure opens new perspectives for the study of cortical visual functions in various disorders where the CSF is impacted, such as amblyopia, traumatic brain injury, and multiple sclerosis.

P3-D-677: Contribution of the auditory and insular cortex to frequency discrimination assessed with neuroimaging

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Background: Recent studies have shown that auditory-tactile stimulation can modulate perception. However, how these sensory modalities interact together remains understudied. Using iEEG recordings, we investigate the contribution of the auditory system and the insula to passive and active pitch discrimination via tactile, auditory and auditory-tactile modalities. Methods: iEEG recordings were obtained from 4 neurosurgical patients. Exp 1. The passive task was a random presentation of 5 deviant stimuli (225, 250, 500, 800 & 1000Hz) among the presentation of a series of standard stimulus (200Hz) through two vibrotactile gloves (Sharp et al., 2019). Exp 2. We used 5 stimuli for the active task (200, 250, 500, 800 & 1000Hz). 80 sequences of 5 stimuli were presented and participants had to determine if the last sound of the sequence was similar or different than the others. Participants did the task under three conditions: auditory only, tactile only and auditory-tactile modalities. Results: Exp 1. iEEG data revealed an activation of the primary auditory cortex and the insula (gamma increase relative to baseline) during tactile perception, and, more importantly, their activity was modulated by deviance

detection. Exp 2. The preliminary results of the active task showed similar results pattern. Conclusion: These findings suggest that pitch discrimination without auditory perception is supported by an interplay between somatosensory, insular and auditory systems. These results provide a better understanding of the interactions between auditory and tactile systems in the human brain.

P3-D-678: Neural speech tracking in spectro and temporally degraded continuous sound

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Speech-in-noise (SIN) perception, the brain's ability to understand speech in the presence of competing noise, is a challenging task that is essential to human functioning in social, vocational, and educational contexts. Certain cognitive processes represent speech with high fidelity and enhance relevant sound features to restore degraded information. A core theory involves a process called "neural speech tracking", whereby low-frequency activity in the brain is aligned with auditorily-rich frequency bands in the speech signal. Specifically, SIN perception relies heavily on the enhancement of temporal (i.e., rhythm) and spectral (i.e., pitch) modulations of an attended speech stream. As such, the comparison between neural representations and a sound's amplitude envelope (1-9 Hz), as well as its frequency following response (80-300 Hz), provides insight into the brain's ability for neural speech tracking. We investigated SIN perception using continuous speech that is either clean, spectrally degraded, or temporally degraded, all with and without the addition of pink noise. Participants engaged in a selective listening task, in which a story (Sir Arthur Conan Doyle's "The Yellow Face") was presented with varying sound quality. An EEG-based sound reconstruction of low and high frequency bands revealed the degree to which the presented sound was encoded, and to which the 'clean' auditory signal was successfully restored. Results from the comparison between different sound conditions will be presented, further elucidating the underlying neural mechanisms behind SIN perception.

P3-E-679: Orexin Receptor Antagonist-Induced Behaviours Across Mouse Estrous Cycle

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The orexin or hypocretin system underlies a wide range of homeostatic and hedonic behaviours. Comprised of orexin neuropeptides which bind G-protein coupled orexin receptors type 1 (OX1R) and type 2 (OX2R), activation of this system modulates wakefulness while pharmacological blockade promotes the physiological conditions of sleep. Orexin signalling itself is regulated by sex, gonadal hormones, and reproductive or estrous cycle phase in female mice. In the current study, adult proestrus female, metestrus female, and male C57BL/6 mice were injected i.p. with 200 µL of vehicle, 24 mg/kg of the OX2R-selective antagonist TCS-OX2-29, or 1 mg/kg of the OX1R/OX2R antagonist TCS-1102. Following injections, all mice underwent behaviour testing for catalepsy, hypothermia, thermal antinociception, and locomotion. Mice were then subjected to a 30-min restraint stress test, after which their anxiety-like behaviour was assessed. Compared to metestrus female mice, those in proestrus with greater estrogenic activity were more sensitive to TCS-1102's cataleptic effects. No other sex- or estrous cycle-dependent

behavioural differences were observed. Next, the brain slices of all mice were immunohistochemically analyzed for region-specific expression of the endocannabinoid synthesizing enzyme, diacylglycerol lipase. This last experiment aimed to characterize the endocannabinoid system's contribution to neuroendocrine-dependent orexin activity. Altogether, these results provide insights on how orexin receptor antagonists differentially affect male and heterogenous female populations. This study was funded by an NSERC Discovery Grant, and a Graduate Teaching Fellowship provided by the University of Saskatchewan College of Pharmacy and Nutrition.

P3-E-680: Activity of Lymnaea stagnalis osphradial neurons is increased by environmental contaminant 1,2-dibromo-4-(1,2 dibromoethyl) cyclohexane (TBECH)

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1,2-dibromo-4-(1,2 dibromoethyl) cyclohexane (TBECH) is a member of the polybrominated flame retardants, many of which have entered the market to phase out their environmentally toxic legacy counterparts. Although its use is not currently regulated by law, prior studies have described its effects as a neurotoxic and endocrine disrupting agent, as well as an obesogen. Indeed, there is a growing body of evidence describing the neurotoxic effects of TBECH, wherein application to rat Purkinje neurons caused a decrease in spontaneous action potential firing, and subsequent studies investigating the mechanism of action found that TBECH blocked voltage gated K+ channels in dissociated neurons of Lymnaea stagnalis. This study aims to establish a high throughput system to characterize neurotoxic effects of environmental contaminants using a bipolar suction electrode to record extracellular signals from the osphradium of L. stagnalis. Perfusing TBECH ([10µM-100µM]) over osphradial epithelia elicited variable responses, predominantly an acute increase in mean firing rate (MFR). Further analysis grouped triphasic events according to matching waveforms within a 5% change in amplitude, filtration of which allowed response detection appertaining to subpopulations of neurons. Increased MFR was observed ubiquitously within a subsect of neurons which accounted for 6-47% of total action potentials elicited over intervals measured, and the increase in MFR ranged variably from 14.8-115.8%. Taken together, these experiments are emblematic of a potential means of biomonitoring neurotoxic pollutants.

P3-E-681: Astrocytic Adipose Triglyceride Lipase (ATGL) regulates glycerolipid metabolism and energy homeostasis

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Astrocytes are the most abundant glial cells in the brain. Modulation of hypothalamic astrocyte activity is known to affect energy homeostasis. Moreover, hypothalamic astrocytes can sense and accumulate lipids. Astrocytes communicate with neurons to transport and store fatty-acids as triglycerides (TG) in lipid droplets (LD). Adipose Triglyceride Lipase (ATGL) is responsible for the first step of triglyceride hydrolysis in LD, thus regulating the cytosolic pool of free fatty acids. We have previously shown that disruption of Acyl-CoA pools in hypothalamic astrocytes alters fatty acid oxidation and esterification in TG, and whole body energy balance. However, the role of astrocytic LD and their hydrolysis by ATGL in energy homeostasis has yet to be studied. We show that primary astrocytes express ATGL and accumulate LD in response to its inhibition. Furthermore, using a viral approach (AAV5-GFAP-Cre-GFP) in chow-fed ATGL flox male mice we show that the loss of ATGL in medial basal hypothalamic (MBH) astrocytes decreases body weight and increases carbohydrate utilisation and glucose tolerance without affecting food intake. This suggests that loss of ATGL in MBH astrocytes impairs nutrient partitioning and

energy balance. Similar studies are ongoing in animals with inducible pan-brain astrocytic loss of ATGL (GLAST-CreER x ATGL flox). Our data shows an unprecedented role for glycerolipid metabolism in hypothalamic astrocytes in energy homeostasis and highlights the importance of astrocytes in the pathophysiology of metabolic disorders such as obesity and diabetes.

P3-E-682: Greywick is a new mouse model for GATA4-associated metabolic subtype of polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the leading cause of female infertility for which there is no cure. It is characterized by reproductive and endocrine dysfunction, with or without metabolic abnormalities. PCOS etiology remains poorly understood, although a central role is suspected for neural crest-derived gonadotropin-releasing hormone neurons from the hypothalamus. Human genetic studies also suggest a role for the GATA4 gene. We generated a new transgenic mouse model for PCOS, named Greywick (Gw) that recapitulate the metabolic subtype of PCOS. These mice bear a neural crest-specific Gata4 promoter-driven RFP reporter, which was randomly inserted in the pseudogene Gm10800. CRISPR-based knockout showed that Gm1800 disruption is not responsible of the PCOS phenotype, which instead appears to be due to knockdown of endogenous Gata4 through promoter competition. In the present study, we aimed to characterize the brain phenotype of Gw mice, and to evaluate the presence of behavioral and microbiota anomalies recently associated with PCOS. We found that the Gata4p[5kb]-RFP transgene in Gw hypothalamus is active not only in GnRH neurons but also in astrocytes. Accordingly, Gata4 is downregulated in both cell types in Gw females. This downregulation is associated with misexpression of genes linked to fertility and obesity. Moreover, Gw mice have anxiety and depression-like behavior and exhibit microbiota alterations. Our model thus represents a new tool to identify the mechanisms involved in PCOS pathogenesis and the development of new therapies.

P3-E-683: Osmotically induced ΔN-TRPV1 translocation in supraoptic neurons

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ΔN-TRPV1 channels are mechanosensitive and are activated in the osmosensitive neurons of the hypothalamus (ONs) by osmotically induced cell shrinkage. This activation increases vasopressin (VP) release from ONs, which enhances water reabsorption at the kidneys to prevent further increases in osmolality. ONs do not undergo acute volume regulation, which enables the ΔN-TRPV1 channels to remain active during short term increases in osmolality. ONs, however, undergo somatic hypertrophy in response to sustained increases in osmolality (e.g., longer than 1 hour), and the mechanisms that maintain ΔN-TRPV1 activity following cell enlargement are not well understood. We used live cell immunocytochemistry to visualize ΔN-TRPV1 trafficking in ONs during sustained increases in osmolality and following recovery. Exposure of isolated ONs to hypertonic solution for 90 minutes caused a

dramatic increase in plasma membrane ΔN-TRPV1 and return to isotonic solution caused rapid internalization of the channels. Translocation and hypertrophy were much greater in ONs isolated from rats deprived of water for 24 hours. Osmotic trafficking of ΔN-TRPV1 channels depends on exocytotic fusion and does not occur in ONs isolated from transgenic mice that lack expression of phospholipase Cδ1 (PLCδ1). Osmotically induced hypertrophy and ΔN-TRPV1 translocation to the plasma membrane may be essential to the adaptation that enables ONs to maintain a high level of VP release during sustained increases in osmolality. These processes may therefore be important in mammalian osmoregulation and may be clinically relevant in the osmotic dysregulation observed in the elderly and chronically ill.

P3-E-684: Estradiol potentiates the fictive breathing response to CO2 in bullfrog brainstems

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Introduction Perturbations of CO2 chemosensitivity contribute to respiratory pathologies, such as sleep apnea, SIDS, and panic disorder. Because CO2 sensing augments at puberty and these disorders show significant sex-based differences, we tested the hypothesis that estradiol (E2) potentiates CO2 chemosensitivity. To do so, we exposed ex vivo brainstem preparations from American bullfrogs (Lithosbates catesbeianus) to E2 prior to testing their fictive breathing response to acute CO2/H+ challenge. Methods We placed isolated brainstem preparations in a recording chamber with circulating artificial cerebrospinal fluid at physiological values (98% O2; 2% CO2; 20°C; pH = 7,90). We placed suction electrodes on cranial nerves V and X to record respiratory-related motor activity. The brains underwent acute (30 min) and chronic (18h) exposure to 10-7 M E2 to test non-genomic and genomic effects of E2, respectively. They were also exposed to hypercapnia (5% CO2; pH = 7,50). All animals were females. Results Time control experiments showed that respiratory-related neural activity remained stable throughout the protocol. There was no acute effect of E2, but chronic exposure doubled the lung burst response to hypercapnia by comparison with the response measured pre-exposure. Conclusion Results show that only the genomic pathway of E2 augments CO2 chemosensitivity. This demonstrates that E2 is a potent modulator of the central CO2 sensing mechanism. Future studies will determine the contribution of α- and β- E2 receptors to this effect.

P3-E-685: Role of orexin neurotransmission in the psychological stress response

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Social isolation (SI) is a chronic stress that increases the risk of numerous diseases, including hypertension, obesity and depression. However, there is limited information pertaining to the neurobiological mechanisms underlying SI. Because orexin (ORX)-producing neurons influence cardiorespiratory and metabolic homeostasis, we hypothesised that SI disrupts ORX neurotransmission

in rats. Adult female and male rats were either kept in standard housing (2/cage, n = 7) or socially isolated (SI; 1/cage, 3 weeks, n = 10). Cardiovascular measurements were obtained by the tail cuff method and corticosterone levels by a multiplex assay. Brains were harvested and Fos-B expression was quantified in the paraventricular nucleus of the hypothalamus (PVN) and the nucleus of the solitary tract (NTS). Double immunostaining was performed using Fos-B on ORX neurons. In SI males, the elevated plasma corticosterone levels and increased number of Fos-B expressing neurons in the PVN compared to controls confirm that SI activates stress pathways. Preliminary results suggest that SI does not activate stress pathways in females. Mean arterial pressure of SI rats was higher than controls; this stress effect was less important in females. In males, SI reduced the number of ORX-labeled cells by 20% but increased the proportion of cells co-expressing Fos-B by 60%. SI also increased Fos-B expression in the NTS of males compared to controls. We conclude that SI activates the stress pathways in a sex-specific manner. This effect, along with enhanced activation of the NTS and ORX neurons likely play an important role in the etiology of hypertension and metabolic dysfunction.

P3-E-686: High salt intake increases RhoA-mDia1 signalling and triggers cytoskeleton reorganization in magnocellular vasopressin neurons

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High dietary salt (HDS) is a major factor contributing to the pathogenesis of salt-sensitive hypertension. Recent studies suggest that central sodium detection mechanisms contribute to increases in the blood pressure following HDS. Changes in plasma sodium are detected by specialized osmosensory neurons located in the hypothalamic supraoptic and paraventricular nuclei (SON and PVN). Under normal physiological conditions, increased plasma sodium activates SON and PVN magnocellular neurons releasing vasopressin (VP), antidiuretic hormone causing renal water retention and vasoconstriction, to achieve fluid homeostasis. Chronic exposure to HDS is associated with excessive osmotic activation of VP neurons, leading to a VP-mediated increase in blood pressure. Magnocellular VP neurons harbor unique cytoskeletal networks comprised of a subcortical actin layer, an array of actin comet-like structures, and an interweaved microtubule scaffold, regulating the sensitivity of neuronal activation. Chronic exposure to HDS increases the actin and microtubule density in VP neurons. mDia1 is the major direct RhoA effector, mediating actin and microtubule polymerization and stability. Our data suggest that RhoA and mDia1 are elevated under the plasma membrane of VP neurons following HDS. Besides, icv administration of mDia1 inhibitor SMIFH2 decreases actin density in VP neurons. We hypothesize that chronic exposure to HDS causes an activation of the RhoA-mDia1 pathway to increase the cytoskeletal density and osmosensitivity of VP neurons, leading to excessive VP secretion, volume expansion, elevated blood pressure, and hypertension.

P3-E-687: Acute exercise erases stress-induced synaptic priming in CRH-PVN neurons

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Neuroendocrine and autonomic responses to stress are critical for survival. Stress imprints the brain to promote adaptations to future stressors and may contribute to maladaptive responses implicated in neuropsychiatric diseases. Multiple plasticity mechanisms have been described, but little is known about how these processes might be reversed. In humans, exercise is used to buffer stress. Here we tested the effects of exercise on synaptic metaplasticity induced by acute stress in corticotropin release hormone cells in the paraventricular nucleus of the hypothalamus (CRH-PVN). We examined the effects of exercise on short-term potentiation (STP) of glutamate synapses on CRH-PVN neurons. We obtained whole-cell patch clamp recordings from mouse CRH-PVN neurons in hypothalamic slices and evaluated the effects of running for 1h after acute stress on STP. Following footshock, high frequency stimulation (HFS) of glutamate synapses on CRH-PVN elicited STP. By contrast, STP was blunted if footshock was followed by exercise. To investigate how exercise affects the downstream neuroendocrine response after stress, we quantified circulating corticosterone (CORT). CORT levels increased 15 min after stress and further increased after exercise. Exercise promotes brain-derived neurotropic factor (BDNF) release. It acts on the tropomyosin receptor kinase B (TrkB) and modulates glutamatergic receptor subunits. We used western blot to quantify protein levels of BDNF, and pGluA1 (AMPA), pGluN2A (NMDA) subunits. We also investigated the role of TrKB receptor activation on stress induced STP and CORT. Our results suggest that exercise may be reversing metaplasticity in the CRH-PVN neurons through the BDNF-TrkB pathway.

P3-E-688: Lateral head impact model of traumatic brain injury causes hyponatremia and activates supraoptic nucleus.

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Background: Hyponatremia is commonly reported in the days following a traumatic brain injury (TBI). Because the brain is highly vulnerable to osmotic swelling, hyponatremia following TBI may result in additional cognitive deficits and functional impairments. One of the most common cause of hyponatremia is inappropriate secretion of vasopressin (VP), which is secreted by the supraoptic nucleus (SON) of the hypothalamus and promotes water reabsorption by the kidney. However, the involvement of the SON in TBI-related hyponatremia has not been investigated yet. Methods: C57Bl/6 male mice aged 2-4 months old were lightly anesthetized with isoflurane and subjected to a lateral head injury using a Gothenburg Impactor (Collision Analysis Inc). This instrument was used to deliver a reproducible, calibrated blow to the side of the head protected by a helmet via a 50 g projectile launched at a velocity of 9 m/s. Mice treated the same way but without the head impact served as controls (shams). The time courses of serum natremia and c-Fos protein expression in the SON after TBI/sham were performed. Results: TBI mice showed significantly lower serum natremia compared to sham at 3h, 6h and 12h after TBI/sham, but not at 24h or 48h. 3h after TBI/sham, our analysis revealed a significantly higher c-Fos nucleus density in the SON of TBI mice compared to sham. c-Fos expression was significantly elevated in both vasopressin and oxytocin cells. This difference was not present 6h after TBI/sham. Conclusion: The SON may be involved in the development of hyponatremia after TBI.

P3-E-689: Lateral head impact does not induce local neuroinflammation and astrogliosis 25 hours later in the supraoptic and paraventricular nuclei of mice

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Introduction: Acute hyponatremia, defined as an abnormally low blood sodium level due to excessive total body water, develops in 29% of traumatic brain injury (TBI) patients and may be caused by excessive release of vasopressin, an antidiuretic hormone that enhances water reabsorption by the kidneys. However, the basis for the prolonged activation of vasopressin-releasing neurons in the supraoptic and paraventricular nuclei (SON and PVN) following an acute stimulus (TBI) remains unknown. Plausible mechanisms include local neuroinflammation and astrogliosis, respectively characterized by an accumulation of microglia (immune cells of the central nervous system) and activation of astrocytes (non-neuronal cells of the central nervous system). Here, our purpose is to determine if there is a local inflammatory response and astrogliosis in the SON and PVN within hours and days following traumatic brain injury in mice. Methods: We compared the immunoreactivity of astrocytic and microglial markers (GFAP and IBA-1) in the SON and PVN of 6 mice 25 hours post-TBI by lateral head impact to 6 control mice. Results: There was no significant difference in GFAP density and microglial count in the SON and PVN of mice 25 hours post-TBI compared to control mice. Conclusion: We found that astrogliosis and local neuroinflammation are not present in the SON and PVN of mice 25 hours post-

TBI. We will further investigate time points prior to and later than 25 hours since these mechanisms may be induced and resolve within 25 hours post-TBI, or be delayed.

P3-E-690: Hypothalamic persistent activity states evoked by stress

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In order to survive, organisms must respond effectively to stress. In order to thrive, however, organisms must recover from the stress and retain salient information about the stressor. Examining neural dynamics of key cell population in the time after stress may offer important insights into how the brain processes stressful experiences, yet we know relatively little about neural dynamics immediately after an acute stress. By measuring local hemodynamics and imaging population calcium dynamics of hypothalamic CRH neurons that coordinate the stress response, we detected an activity pattern that is evident exclusively after a threat. Recording calcium signal from individual CRH neurons in vivo revealed a stable activity state that persists for minutes after exposure to footshock. This persistence does not reflect an increase in activity of the population that exhibits a slow recovery function. Rather, computational techniques revealed that this post stress activity represents a persistent activity state that is distinct from the resting state observed prior to the threat exposure. We propose that the post-stress persistent activity state may represent a critical period that promotes adaptive coping behaviors and allows organisms to process and retain information about the aversive experience.

P3-E-691: Triglyceride Metabolism in AgRP neurons Regulates Feeding Behavior and Peripheral Metabolism

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Background: Lipid (e.g. triglyceride, TG) metabolism in hypothalamic neurons is involved in whole-body energy homeostasis. Adipose Triglyceride Lipase (ATGL) catalyzes the first step of TG hydrolysis in lipid droplets (LD) and is expressed in POMC and AgRP neurons of the arcuate nucleus (ARC) that control energy balance. We investigated the regulation of neuronal TG and LD by ATGL and its role in the control of energy homeostasis. Results: We found that ATGL promotes TG lipolysis from LD in hypothalamic neurons. In the ARC, ATGL expression is upregulated by cold exposure, fasting and enriched in orexigenic AgRP neurons suggesting that ATGL plays a role in adaptive feeding responses to metabolic challenges. Knockdown of neuronal ATGL in C. elegans and male, but not female, D. melanogaster inhibits peripheral fat breakdown, suggesting that neuronal ATGL promotes peripheral lipolysis in a sex specific manner. In male mice, ATGL knockout specifically in ARC or AgRP neurons affects energy expenditure, feeding behavior (meal pattern) and thermoregulatory responses to cold, suggesting decreased AgRP tone. Such

changes were not observed in female mice nor in mice with ATGL KO in POMC neurons, highlighting a male-specific regulation of energy homeostasis by ATGL in AgRP neurons. At the cellular level, lipidomic, metabolomic, electrophysiology and morphology studies in hypothalamic neurons demonstrate an ATGL-dependent remodeling of TG and membrane phospholipids, intracellular metabolism and neuronal activity. Conclusion: Taken together, our findings reveal a previously unrecognized role for ATGL in neuronal lipid metabolism and regulation of whole-body energy homeostasis by AgRP neurons.

P3-E-692: The effects of acute non-discriminatory social defeat stress on male and female mice.

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Stress is a common risk for developing depression/anxiety; disorders seen more in females than males. However, research using animal models of social stress have mainly included males. A new chronic stress paradigm - chronic non-discriminatory social defeat (NDSD), based on the social defeat stress model - has recently been developed, producing comparable stress effects in male/female mice. In this project, we sought to find endocrine/brain activation effects of acute NDSD on male/female wildtypes (WT) and mice with mutations to the growth hormone secretagogue receptor (GHSR KO) - a 7-TM receptor in stress-related brain regions. Male/female pairs were added to the cage of a CD-1 bully for 10 min. The bully aggresses towards both intruders. They are then separated and sacrificed. Groups were chosen by genotype, estrus cycle phase, and sex. As expected, acute NDSD led to increased plasma corticosterone levels compared to controls. Notably, stressed, WT and KO males showed higher cort. levels than females. Using cFos as a marker for neuronal activation, we found stress increased PVN activation in all groups. In females, KO mice sacrificed pre-ovulation showed a higher cellular response to stress than WT counterparts, but not those sacrificed after. All stressed mice showed higher cFos expression in the ArcN than controls, but all females showed higher cFos density than males in both groups. These data show a differed response to an acute social stressor in males/females and suggests that in the female PVN, stress-induced activation is moderated by GHSRs and possibly estrogen.

P3-F-693: Mismatch negativity contributes to auditory mnemonic discrimination in aging

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The mismatch negativity (MMN) is an event-related potential associated with perceptual change-detection. Whether the MMN extends beyond an index of perceptual discrimination and correlates with higher-order cognition, such as episodic memory, is unclear. To what extent does perceptual discrimination, indexed by the MMN, contribute to subsequent memory for those same stimuli? Furthermore, how does this relationship change in aging? We hypothesized that the MMN, generated by incidentally encoded auditory stimuli, would be correlated with younger and older adult participants' ability to discriminate those stimuli (targets) from highly similar lures and from dissimilar foils. We

measured the MMN in 30 younger adults and 26 older adults using a passive auditory oddball task with standard and deviant pure-tone sequences differing in pitch contour. After exposure, all participants completed an incidental memory test for targets, lures, and foils. As expected, participants at test exhibited high sensitivity at recognizing target items relative to foils. Within our younger adult sample, we found a significant correlation between MMN amplitude and lure discrimination, but not with foil discrimination. Preliminary analyses with older adults show evidence for null correlations with memory performance. Findings suggest that the MMN of younger adults relates to recognition memory, particularly mnemonic discrimination. Our investigation shows that our capacity to discriminate sensory inputs, as measured by the MMN, translates into precision in memory.

P3-F-694: Cognition moderating the response to a CBT-based personality targeting intervention for adolescent suicidal ideation.

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Suicide is a major cause of death among 15-29-year-olds, accounting for the fourth highest number of deaths in this age group. To address this issue, school-based prevention programs have been developed and showed encouraging results. The PreVenture program, which targets high-risk adolescents' personalities to delay and/or reduce substance use, has shown a decrease in suicidal ideation over two years. However, there have been few studies on how these interventions work in young adolescents, especially regarding factors that could influence their effectiveness. This project aimed to examine how to determine which adolescents will benefit the most from the PreVenture intervention in terms of reducing suicidal ideation. High-risk adolescents were screened using the Substance Use Risk Profile Scale and then randomly assigned to either the intervention or control group. They were monitored for two years after receiving or not receiving the PreVenture intervention. A moderation analysis was performed using a latent growth model with MPlus, with four baseline measures of cognition being tested: spatial working memory, delayed recall memory, inhibitory control, and IQ. Controlling for sex and socio-economic status, the results showed that only baseline delayed recall memory was significant, with those with poorer baseline delayed recall memory benefiting the most from the intervention in terms of reducing suicidal ideation over time. In conclusion, these findings provide valuable insights into how to enhance the effectiveness of these prevention programs, supporting the implementation of school-based interventions and contributing to the overall prevention of suicide.

P3-F-695: Circadian clock genes in the nucleus accumbens control alcohol consumption in mice

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Circadian clock genes play a central role in the generation and regulation of circadian rhythms, thus affecting various cellular, physiological, and behavioral processes. Moreover, their contribution to a broad range of physiological, metabolic, and behavioral disturbances and disorders, including alcohol use

disorder, is well described. Recently, the striatum has been identified as a site of sex-specific regulation of alcohol consumption through the action of circadian clock genes Bmal1 and Per2. However, information on the region-specific contribution of these clock genes within the striatum on alcohol consumption is missing. Although all major striatal subregions have been implicated in the control of alcohol consumption in various forms, the nucleus accumbens (NAc) is distinguished by its critical role in reward and appetitive motivation. Therefore, we conditionally ablated Bmal1 and Per2 from cells of the NAc in male and female mice and studied alcohol drinking behavior. Both, males and females with a conditional Bmal1 knockout in the NAc consumed more and had a higher preference for alcohol than control animals. In contrast, only male mice with a conditional Per2 knockout consumed more alcohol and displayed a higher preference, whereas females did not differ from their control counterparts. We therefore hypothesise that Bmal1 and Per2 in the NAc inhibit voluntary ethanol consumption in males through a shared mechanism, whereas in females, only Bmal1 has and inhibitory function on alcohol consumption.

P3-F-696: Effects of chronic in utero exposure to thiamethoxam in the rat

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Neonicotinoid pesticides are the most widely used class of insecticides worldwide and have traditionally been considered safe because of a selective action on the insect neuromuscular junction (NMJ) with minimal effects on vertebrate NMJs. The subunit composition of nicotinic receptors in the mammalian CNS, however, differs from those in the periphery. Our aim was to determine if exposure to thiamethoxam in utero resulted in detectable changes in the offspring both pre-weaning and as adults. Timed pregnant CD1 rats (N=12) were implanted with osmotic mini pumps (Alzet 2ML)(drug or vehicle from GD14-21). Litters were culled to n=10 (5 male, 5 female where possible) and left with the dam until weaning. Beginning on PND8 pups were tested on a 12 point neurodevelopmental test battery until PND20. In adulthood a subset of pups from each litter were tested in an Elevated Plus Maze and Y-Maze and post-mortem brain tissue was processed for expression of NMDA, GABA and nACh receptor subunits. Data were analyzed using litter as the unit of variance. Results indicated no significant treatment effects on neonatal development. Data in adult offspring revealed a significant anxiolytic effect in drug treated male rats with a similar, but not significant difference in females. Y-Maze performance did not change with treatment. Quantitation of protein expression is in progress. We conclude that in utero exposure to thiamethoxam produces no changes in physical or sensorimotor development but alterations in adult behaviour warrant further investigation. Supported by NSERC

P3-F-697: Multi-site characterization of dopamine signals for reinforcement

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The dopaminergic system enables associative learning by signaling the expectation and valence of a reinforcement. Previous studies have identified heterogeneous reinforcement signals in axons of dopaminergic neurons projecting to various structures along the mesolimbic, mesocortical and nigrostriatal pathways. Yet, a characterization of the actual dopamine release in response to this axonal activity is missing. Here, we recorded the temporal dynamics of an improved fluorescent dopamine sensor (GRAB-DA3) using multi-site fiber photometry in head-fixed mice trained to associate a tone with reward. With this approach, we compared dopaminergic signals in the medial prefrontal cortex, striatum (dorsal and tail), nucleus accumbens (core, lateral and medial shell) and the olfactory tubercle. Our preliminary results indicate that unexpected reward triggered dopamine release in all the output regions recorded. This release varied in sizes, especially in the prefrontal cortex that showed small, yet statistically significant, dopamine response to reward, and varied in temporal dynamics, especially in the dorsal striatum that showed the fastest response. Dopamine signals for punishment were small in most of the recorded targets, however the prefrontal cortex presented a larger signal in comparison to reward. Together, our results illustrate the level of heterogeneity by which dopamine signals key features of reinforcement learning along the dopaminergic system.

P3-F-698: Tomorrow is another day: Baseline neural activity in fronto-parietal reach areas drifts over time but resets daily

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During electrophysiological recordings, the baseline level of neural activity may drift due to factors that are not directly related to a behavioural task. These may be internal (e.g., motivation, satiation, fatigue), external (e.g., ambient noise), or mechanical (e.g., tissue damage, loss of isolation). Studying internal or external factors requires precise experimental manipulations, but the effects of mechanical factors should be observable in multi-day recording data. For example, changes due to tissue damage or a loss of isolation should be monotonic over time, even across multiple days. We analysed well-isolated neurons recorded over multiple days in dorsal premotor (PMd) and posterior parietal cortex (PPC) of two monkeys performing a delayed reach decision task. We compared the baseline firing rate measured during the 200 ms pre-stimulus epoch across time in each daily session and across sessions. We found that 68% (136/200) of PMd cells and 45% (77/173) of PPC cells exhibited a change in the baseline as a session progressed. Of these, most cells had a decreasing baseline (PMd: 73/136, 54%; PPC: 43/77, 56%), many others had an increasing baseline (PMd: 53/136, 39%; PPC: 30/77, 39%), and few had mixed responses (PMd: 10/136, 7%; PPC: 4/77, 5%). Importantly, these changes appeared to "reset" daily, such that the drifted baseline reverted to a similar level at the start of each new day. Thus, they are unlikely due to tissue damage or a loss of isolation. Instead, we suggest that they may reflect more internal factors, such as the monkeys' decreasing motivation.

P3-F-699: Effect of vascular burden and menopause status on episodic memory

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Literature shows that menopause and vascular burden (VB) are associated with age-related decreases in memory and cognitive functioning in some females (Armstrong et al., 2019; Marchant et al., 2022). Yet, the link between these variables has not been directly investigated. In the present study we tested females on an episodic memory task and collected blood samples to assess VB. We created a weighted composite score composed of subjects' LDL, total cholesterol and Apolipoprotein B measurements to measure VB. Participants were grouped as: (1) premenopausal (n= 79, Agemean = 34.5, Agesd = 9.4), (2) perimenopausal (n= 35, Agemean = 50.6, Agesd = 4.1) and (3) postmenopausal (n=42, Agemean = 57.5, Agesd = 4.4). We ran multiple linear regressions to determine if 1) menopause predicted VB, and 2) menopause, VB, and their interaction predicted episodic memory. Education was included as a covariate in all models. Results revealed menopause predicted VB (ß = -0.437, < 0.001), yet only menopause status significantly predicted memory accuracy (ß = -0.410, $p < 0.001$) and RT (ß = 0.322, $p < 0.001$). Our results suggest that factors related to menopause may better explain mechanisms underlying cognitive decline in women compared to VB.

P3-F-701: Contrast Detection in Noise in Healthy Vision and Visual Snow Syndrome

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The detection of low-contrast targets can be understood as being limited by an internal noise in the visual system. In normal vision, this noise is not usually perceived. Visual snow syndrome is a neuro-ophthalmological disorder in which individuals report seeing flickering dots across the entire visual field. We hypothesise that this condition may reflect an abnormal internal noise state in these individuals. In this study we investigated visual internal noise and adaptive changes to that noise in both normal vision and in visual snow syndrome. We made use of the equivalent noise method. This measures the amount of external noise that must be applied to a stimulus to be equivalent to the internal noise in the visual system. This gives an objective measure of both i) the effective "noisiness" of input to visual processing, and ii) the efficiency with which that noisy information is processed. We measured contrast detection thresholds for detecting different grating targets (sin-wave, square-wave, and the square-wave with a missing fundamental) both with and without simultaneous spatial noise (spectrally pink or white). The contrast of this noise was set as a multiple of the participant's contrast threshold for detecting it. Preliminary results show that participants with visual snow syndrome have lower detection thresholds for white noise than control participants. In our noise-masking data, there is no significant difference between the equivalent noise and efficiency parameters from control and visual snow participants. These preliminary results suggest that visual snow is not due to an elevated noise in the visual system, but instead may result from a failure of a process that usually suppresses internal noise from awareness.

P3-F-702: Corticotrophin releasing factor, central amygdala, and their role in memory modulation by opioid withdrawal

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AIM: It has been recently demonstrated that opioid withdrawal facilitates memory consolidation. To further understand the neurobiology of this phenomenon, the current study focused on corticotrophin-releasing factor (CRF) and the central amygdala (CeA) because of their known involvement in opioid withdrawal and memory functions. METHODS: Male Sprague-Dawley rats were implanted with osmotic mini-pumps releasing 3.5 mg/kg/day heroin and received injections of 3 mg/kg naloxone (NLX) preceded either by systemic injection of 10 - 20 mg/kg antalarmin (CRF 1 receptor antagonist) or intra-CeA infusions of 0 - 2 ug antalarmin immediately after the sample phase of spontaneous object recognition (SOR) task. RESULTS: It was found that both systemic and intra-CeA infusion of antalarmin blocked the memory-enhancing action of NLX-precipitated withdrawal. CONCLUSIONS: These experiments suggest the memory enhancing action of drug withdrawal could promote the permanence of addictive actions through a mechanism that involves neurotransmission of CRF in the CeA.

P3-F-703: Intermediate CA1 is necessary for object-in-place recognition memory in mice

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The ability to associate the identity of an object with its spatial location is vital in performing basic behaviours such as retrieving food, finding shelter, or identifying predator cues. Spontaneous object-in-place (OiP) recognition memory tasks are commonly used in rats to assess this identity-location association. This behavioural task is commonly used to characterize cognitive deficits in rat models of neurodevelopmental disorders such as schizophrenia and autism spectrum disorders. Importantly, while mouse models have been widely adopted in behavioral and systems neuroscience research for their ease of genetic manipulations, very few studies have successfully assessed OiP recognition memory in mice. To address this limitation, we tested distinct experimental designs of the spontaneous OiP recognition task in adult naïve C57/129J and C57BL/6J mice. Mice were able to successfully perform the two-object, but not the four-object version of the OiP task, with retention intervals of five minutes and one hour. Using chemogenetic inhibition, we investigated the contribution of the hippocampal intermediate CA1 (iCA1) and medial prefrontal cortex (mPFC) to two-object OiP. We found that the iCA1, but not the mPFC, is required for the expression of an allocentric version of the two-object OiP task with a five minute retention interval. Our data establish guidelines for successful assessment of OiP recognition memory in two commonly used laboratory mouse strains, and expand our understanding of the neural basis of object location-identity associations in mice.

P3-F-704: Laminar microcircuitry underlying target selection in marmoset posterior parietal cortex

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Investigations in primary sensory cortex have suggested a canonical laminar circuit shared by all areas of neocortex. In frontoparietal networks, studies in macaques have revealed neurons with roles in visual attention and oculomotor control. Knowledge of the laminar microcircuitry underlying these processes remains limited, as laminar recordings in key nodes of this network are difficult due to their locations

deep within sulci. To address this gap, we exploited the relatively lissencephalic cortex and homologous frontoparietal networks of the common marmoset. We used Neuropixels probes to carry out ultra-high density laminar recordings in the posterior parietal cortex (PPC) of two adult marmosets while the animals completed a visual target selection task in which they were required to saccade to a target in the presence or absence of a distractor. Overall, we recorded the activity of 1397 single units, of which 463 exhibited significant visual or saccade related activity. Of these,193 discriminated between target and distractor stimuli. To investigate whether aspects of the selection process varied with cortical depth, we determined the putative cortical layer for each recorded neuron using an established spectrolaminar pattern and determined visual onset and target discrimination times. We observed visual activity first in layer 4 while target discrimination was first observed in layers 2/3. Taken together, these findings support a model of cortical circuitry in which visual inputs arrive first in layer 4 while layers 2/3 facilitate target discrimination.

P3-F-705: Tracking place field evolution across days during object-location associative learning

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Hippocampal place cells demonstrate context-dependent spatial representations of their environment in subjects that have been well-trained on a navigation task. How these representations evolve with learning is seldom studied, particularly in more complex tasks that are gradually learned over many days or weeks. Using one-photon calcium imaging with micro-endoscopes (miniscopes), we tracked hundreds of cells in dorsal CA1 of the hippocampus of mice gradually learning a paired-associate learning (PAL) touchscreen task. Generalized linear models of single-cell activity in relation to spatial and contextual variables revealed specific ensembles of cells that dynamically evolve their tuning to spatial and contextual variables over more than a month of daily training on the touchscreen task, from habituation to overtraining phases of learning. Individual cells became transiently tuned to task context during specific bouts of learning, developing context-specific place fields that then generalized across contexts gradually as the animal became over-trained on the task. The data suggest that learning might transiently promote the formation of context-dependent maps in the hippocampus, which are then consolidated as the subject is over-trained and becomes familiar with the task design.

P3-F-706: Chronic cocaine impacts probabilistic reversal learning

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Chronic exposure to drugs of abuse leads to long-lasting cognitive impairments. Here we characterized the impact of chronic cocaine on decision-making in mice using a probabilistic reversal learning task (PRL). Our data support the hypothesis that chronic cocaine reduces cognitive flexibility. Wild-type male and female mice were trained to press two levers armed with either a 20% or 80% probability of delivering sweetened-condensed milk into a fluid port for oral consumption. Reinforcement probabilities were reversed each time after 8 consecutive presses on the higher probability lever. Well-trained mice

completed 21 testing sessions, and they received daily injections of either cocaine (20 mg/kg) or saline after completing sessions 8-14. Injections of cocaine decreased the number of reversals performed per session. Cocaine-injected mice had a lower probability of earning rewards, indicating that they are using a less efficient strategy. This effect was led by an increase in the acquisition error and win-shift probability. No sex-differences were detected. This experiment shows that chronic cocaine exposure negatively affects the cognitive flexibility of mice on a PRL task, despite never being testing while on the acute effect of cocaine. These impairments may reflect important differences in the decision-making strategies of chronic cocaine users. The increase in win-shift probability is consistent with there being a decreased sensitivity to positive reinforcers. In future studies, we plan to characterize how changes in dopaminergic activity in the striatum underly this effect. A better understanding of decision-making differences and their neural correlates should help inform drug treatment efforts.

P3-F-707: Social behaviour differentially engages the dorsal medial frontal cortex in degus, but does not increase coupling to hippocampal theta

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Brain oscillations provide a temporal structure to neural activity that organize communication within and between regions. One example is the 6 to 10 Hz "theta" oscillation, found prominently in the mammalian hippocampus during movement and attention, and likely important for stitching together sequentially-activated neural assemblies. The role theta plays in social cognition and memory has not been thoroughly examined. We tested whether regions of frontal cortex become more synchronized with hippocampal theta during dynamic, unconstrained social interaction by recording physiologically from four degus during a series of behavioural epochs. In prior work we have shown that degus are highly gregarious and readily establish relationships with new individuals, offering an opportunity to assess the mechanisms supporting peer recognition and relationship formation. We find that, as with other mammals, the degu hippocampus exhibits higher-frequency (Type 1) theta during locomotion and lower-frequency (Type 2) theta during static attention. Neuron population activity and the local, 40-70 Hz gamma oscillation increased in frontal cortex during social relative to non-social conditions. Social epochs were not, however, characterized by higher hippocampal theta, nor higher synchronization of frontal neuron activity with theta. The results are consistent with previous studies linking medial frontal cortex to social behaviour, but suggests this does not necessarily involve differentially higher communication with the hippocampus.

P3-F-708: Emotional gaze cuing impacts temporal order judgements for gazed-at targets

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Our attention is spontaneously oriented towards locations where others are looking. This is especially true when a face displays an emotional expression. While this so-called gaze cuing effect has been shown to be adaptive for many aspects of cognition, it remains relatively unknown how it might impact our perception of time. Using a modified gaze-cuing paradigm, we presented participants with a central gazing face which maintained a neutral expression or reacted emotionally with a fearful or happy expression. Two peripheral targets were then presented on the left and right side of the face, with a temporal offset between them. Participants were asked to report which target appeared first. Accuracy performance slopes were calculated for participants' temporal precision as a function of the face's emotional expression and the first target's gaze congruency. Participants made better temporal order judgements when the first target appeared on the gaze-congruent side, but this effect depended on the face's emotional expression. While the congruency effect was present for fearful faces, it was not present for faces with neutral expressions. These data suggest that attention orienting from emotional faces may enhance temporal precision of target perception at the gaze-congruent location. This may reflect an adaptive feature of gaze-cuing, which allows us to respond quickly to the locations that our peers indicate are emotionally significant.

P3-F-710: VTA dopamine neurons drive learning through valence-based prediction error

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The phasic firing of ventral tegmental area (VTA) dopamine (DA) neurons is established as signalling prediction error to support learning about reward. However, evidence for the role of DA in learning about aversive events remains mixed. In fact, it is still debated whether this signal drives learning across reward and aversion through a common "valence-free" error, relying on outcome salience, or a signed "valence-based" error, relying on outcome value. In other words, if DA neurons show excitation to both rewarding and aversive events, or if they show excitation to reward and inhibition to aversion. We addressed these questions using behavioral electrophysiology and optogenetics. First, we recorded single-unit activity of VTA DA neurons in freely-moving rats performing a conditioning task, where auditory cues were paired with either aversive footshock or sucrose reward. We found that DA neurons form two distinct populations coding for cue identity and valence-based prediction error (i.e. excitation to reward-cues; suppression to shock-cues). To determine if the suppression of DA neurons to shock-predictive cues is causal to learning, we enhanced this signal using optogenetic inhibition of VTA DA neurons. Rats underwent a second-order conditioning design: In phase 1, a cue was paired with footshock (S1-shock); in phase 2, a novel cue was paired with S1 in the absence of footshock (S2-S1); in a manipulation-free test, fear to S2 was probed. Optogenetic inhibition of DA neurons at the onset of S1 on S2-S1 trials led to enhanced learning about S2, evidenced by greater fear to S2 on test compared to control. These data settle that VTA DA neuron activity represents a prediction error signal that includes outcome valence to drive learning.

P3-F-711: The effects of a Mediterranean-based diet on anxiety-like behaviours in postpartum dams stressed during pregnancy

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It has been suggested that adherence to healthy dietary patterns during the perinatal period, such as those based on the Mediterranean diet, could improve mental health at postpartum. Using a mouse model of maternal stress, we examined whether a perinatal diet based on human Mediterranean patterns limited behaviours suggestive of anxiety and of depression at postpartum. Female C57BL/6N mice were fed a Purified (Control) or an in-house Mediterranean-based (Purified enriched with olive and fish oils, fruits, vegetables, pulses, and walnuts) diet starting two weeks before mating and remained on their respective diets until behavioural testing. Dams experienced a physical restraint stressor during the second trimester (Embryonic Days 7.5-12.5) or were not manipulated. During the two days that followed weaning, anxiety- and depressive-like behaviours were assessed using the elevated plus maze, open field, and tail suspension tests. Stressed dams fed the Mediterranean-based diet expressed less behaviours suggestive of anxiety in the elevated plus maze than their counterparts fed the Purified diet. In contrast, passive coping behaviours in the tail suspension test were not affected by the maternal stressor or the dietary intervention. These findings indicate that adherence to a Mediterranean-based diet during pregnancy and lactation could promote better mental health outcomes at postpartum and

provide preliminary support for the development of dietary recommendations to improve mental health during the perinatal period.

P3-F-712: Noradrenergic modulation of mouse cortical interneurons and its effect on learning

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The noradrenergic system impacts learning by influencing cortical activity through a dense network of noradrenergic axons. However, the way by which noradrenaline modulates the distinct cellular components of cortical circuits remains poorly characterized. We aim to identify the subtypes of cortical interneurons targeted by noradrenaline and how they shape inhibitory activity during various stages of learning. By analyzing the patterns of expression of alpha1-, alpha2- and beta-adrenergic receptors from a transcriptomic cell-type atlas of the mouse cortex, we found that alpha1 receptors are heavily enriched in inhibitory neurons. To investigate the spatial distribution of these expression patterns, we labeled the mRNA of noradrenergic receptors and interneuron subtypes. Our preliminary results show higher levels of alpha1 receptor mRNA in Vip and NDNF positive interneurons of the superficial layers. Alpha1 receptor subunits a and b are differentially expressed in these interneurons, with the ratio of alpha1a to alpha1b expression peaking in NDNF+ cells compared to Vip+ cells. We are currently extending these experiments to include other neuronal subtypes and noradrenergic receptors. Future experiments will evaluate how the expression of noradrenergic receptors affects interneuron activity during the learning of a sensorimotor task. Thus far, our results suggest that noradrenaline modulates cortical circuits by differentially targeting Vip+ and NDNF+ cortical interneurons.

P3-F-713: Optogenetic stimulation of basolateral amygdala neurons invigorates reward-seeking evoked by sucrose-associated discriminative and conditioned stimuli in female and male rats

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The basolateral amygdala (BLA) mediates reward-seeking that is under the control of conditioned stimuli (CSs). Discriminative stimuli (DSs) are fundamentally different, as they signal reward availability (DS+) or unavailability (DS-). The BLA's role in DS-evoked reward-seeking has rarely been studied. Here, we determined whether optogenetic stimulation of BLA neurons mediates reward-seeking evoked by a sucrose-associated DS+ and CS. Female and male Sprague Dawley rats were trained to discriminate between a 1-min DS+ (cue light) during which lever presses produced liquid sucrose delivery paired with a 5-s CS (distinct cue light + tone), and a 1-min DS- (flashing light) that signaled sucrose unavailability. We next examined the effects of optogenetic stimulation (ChR2-eYFP; 465 nm, 20 Hz, 10 mW, 5 ms pulses) on BLA neurons during non-contingent and response-contingent cue presentations on sucrose-seeking. Non-contingent DS+, but not CS or DS-, presentations increased sucrose-seeking. Response-contingent presentations of either the DS+ or CS evoked high levels of sucrose seeking. Photostimulation of ChR2-expressing BLA neurons did not impact sucrose-seeking evoked by non-contingent cue presentation, regardless of cue type, but it did invigorate sucrose-seeking triggered by response-contingent presentations of the DS+ and, to a lesser degree, the CS. Thus, the BLA mediates reward-seeking

controlled by a DS+ and CS, an effect that may be more robust with the DS+. This finding illustrates a neural mechanism that drives the capacity for unique cue-controlled reward-seeking behaviour.

P3-F-714: Pattern separation in aged male and female rats

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Pattern separation is a key component of episodic memory and reduces the overlap between neural activity that represents similar experiences. This process is thought to be dependent on the dentate gyrus granule cells in the hippocampus; however, there has been few studies outlining the differences in pattern separation in older males and females. 26 Sprague-Dawley rats (13 males, 13 females; 11-12 mo) were tested in two pattern separation tasks. First, the two-trial spatial Y-maze test and then the spontaneous location recognition (SLR) task were performed twice at dissimilar (simple) and similar (difficult) levels in a circular and then a square arena. The Y-maze test consists of two trials where the rat is allowed to freely explore the two of the three arms and then at the second trial, the rat is returned to the maze and all three arms are accessible to explore. The SLR task measures how well animals can distinguish between and recall the locations of objects that are shown during the encoding phase. In Y-maze, there were no sex differences in the numbers of rats who entered the novel arm first during the second trial (10 out of 13). However, female rats spent significantly more time in the novel arm compared to familiar arm, while in male rats the time spent in novel and familiar arms did not differ notably. Females were more active based on the total distance travelled in the maze. In SLR task, discrimination ratios in females and males were not significantly different and did not show any preference for novel or familiar location in either the circular or square open field mazes. Collectively, this study found female rats retained memory for a spatial y-maze task but could not conclusively determine sex differences in aged rats in the SLR task.

P3-F-715: 22q11.2 (Del 3.0) deletion syndrome as rodent model to assess working memory performance in schizophrenia

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Schizophrenia (SZ) is a neuropsychiatric disorder associated with impairment in cognitive processes such as working memory (WM), which are unable to be modulated by conventional treatments. To assess SZ in the preclinical setting, animal models that have been generated to recapitulate key genetic risk factors for neuropsychiatric disorders are valuable tools to investigate the mechanisms that underlie cognitive symptoms. We assessed a new mouse line that reproduces the 3.0-Mb deletion of the 22q11.2 deletion syndrome (Del 3.0), which is the strongest genetic predictor of developing SZ. Deficits in working memory are a central phenotype of SZ, so we assessed working memory performance in this line using the touchscreen-based trial-unique non-match to location (TUNL). After a delay period (2s, 3s, 4s), mice must distinguish between a location matching the sample location and a non-matching stimulus location presented on a screen and are rewarded if the novel non-matching location is chosen. Del 3.0 mice were different compared to wild-type mice in several measures including accuracies and latencies to respond to both the correct and incorrect stimulus. In the 4s delay, both female and male Del 3.0 mice showed a

significantly higher latency to respond to the correct stimulus. A similar response was observed in the latency to respond to the incorrect stimulus in female Del 3.0 mice in all the delays assessed, and in male Del 3.0 mice in 3s and 4s delays. These findings suggest that Del 3.0 mice present an abnormal profile on the TUNL task.

P3-F-716: Chemogenetic Excitation/inhibition of Prefrontal Cortex projections to The Nucleus Accumbens and Cue-induced Cocaine Seeking Behaviour in Female Rats

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Cocaine addiction involves relapse to drug use, often triggered by drug-associated cues. Drug cues can be conditioned stimuli (CSs) that occur after drug intake and that are paired with drug effects. Drug cues can also be discriminative stimuli (DSs), which are present independent of drug seeking actions, and that inform about drug availability. Infralimbic cortex (IL) projections to the nucleus accumbens (NAc) shell and prelimbic cortex (PrL) projections to the NAc core mediate CS-triggered cocaine relapse. It is not known how these circuits may mediate DS-triggered cocaine relapse. We aim to compare the effects of activation of IL-Shell neurons and inhibition of PrL-Core neurons on DS and CS-induced relapse after intermittent cocaine use. Thus, we will use viral-mediated gene expression of designer receptors exclusively activated by designer drugs (DREADD) in target neurons, and then activate/inhibit these neurons with CNO. Female Sprague-Dawley rats will self-administer cocaine. During each session, a discrete cue light (DS+) will signal drug availability, a different cue light will signal drug unavailability (DS-), and each cocaine infusion will be paired with a light-tone stimulus (CS). Three weeks after the last self-administration session, we will assess DS and CS-induced cocaine seeking following CNO or aCSF injections into the NAc core or shell. The findings will determine the respective roles of distinct corticoaccumbens circuits in DS and CS-induced relapse after abstinence. This work could inform targeted neuronal manipulations as anti-addiction treatments.

P3-F-717: Effect of temporal characteristics of noise on equivalent noise and efficiency.

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Internal noise in the visual system limits low-contrast target detection. The equivalent-noise paradigm quantifies the effective internal noise levels by adding external noise until detection performance drops. Sampling efficiency can be calculated using the linear amplifier model (LAM) and compared to the ideal task performance. These methods show changes in perceptual limits across development or disease states. This study investigates whether the visual system uses different techniques to detect a target grating in noise with varying temporal features. Sinusoidal gratings were detected in 1-D pink spatial noise. This noise was presented with 3 temporal spectra (constant, pink, white) and at 3 levels (both without noise, and with noise +12dB, and +18dB above the threshold for detecting the noise itself). A 2-interval forced choice task (intervals: noise only, noise + grating) was used. We generated noise masking functions, and equivalent internal noise and efficiency were fitted using the LAM. Mixed-effects models were used to analyze the repeated-measures data, and there was no significant main effect of temporal noise condition on efficiency or equivalent noise. We find that when stimulus contrast is quantified as

RMS the performance is stable across temporal conditions. We compare this behaviour against performance from ideal and sub-ideal models of the task. Planned future studies will test various stimulus presentation durations and compare the efficiency and equivalent noise of young adults to those of older adults.

P3-F-718: Physiological reactivity in acting: exploring the effects of traumatic narratives on emotional arousal

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Actors are expected to move their audiences by delivering emotional narratives. Headphones verbatim is a technique in which actors listen to pre-recorded testimonies (often about real traumatic events) through headphones and deliver the words as they hear them live. Psychological trauma can occur through indirect exposure to traumatic events. Thus, we need to identify techniques to better protect actors. This study aims to examine the emotional experience of actors when performing real testimonies of sexual violence using the "headphones verbatim" technique. Heart rate variability, skin conductance response and pupil diameter are recorded while neurologically healthy actors deliver emotional and neutral narratives according to 'technical' or 'content' instructions. Technical instructions focus on the articulation of the narrator. Content instructions ask participants to imagine being the narrator. We hypothesize that lower heart rate variability, and greater skin conductance response and pupil diameter will be observed when actors perform emotional as compared with neutral narratives., which would indicate that emotional responses can be generated and captured in a semi-naturalistic theatre performance environment. We also expect to see lower emotional arousal using the technical instructions compared to the content instructions when performing emotional narratives, which would demonstrate that physiological reactions can be voluntarily modulated via listening strategies. Our findings may contribute to safer acting practices, but could also be useful for other professionals, such as psychotherapists and emergency dispatchers.

P3-F-719: Sex-specific effects of a Mediterranean-based diet on depressive-like behaviours and colonic tryptophan metabolism in a mouse model of prenatal stress

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Prenatal stress may increase the risk for depression in offspring and it has been suggested that this could occur through the alteration of intestinal bacteria and enzymes involved in tryptophan metabolism. Dietary patterns based on the Mediterranean (Med) diet, that include foods rich in nutrients involved in the tryptophan-serotonin pathway, have been linked to a reduced incidence of depression and to symptom improvements when used as an intervention. Using a mouse model, we examined the efficacy of a Med-based diet in preventing behavioural impairments and intestinal changes in tryptophan metabolism resulting from prenatal stress in female and male offspring. Pregnant C57BL/6N dams fed a Purified (Control) or a Med-based (Purified enriched with olive and fish oils, fruits, vegetables, legumes,

and walnuts) calorie-matched diet experienced a physical restraint stressor during the second trimester or were not manipulated. Weaned female and male offspring remained on their respective diet until adulthood where their depressive-like behaviours were tested and their colon was collected (Postnatal Days 67-70). The Med-based diet reduced immobility in the tail suspension in prenatally stressed females but modulated the colonic expression of enzymes involved in tryptophan metabolism and of 5-HT receptors predominantly in males. These findings suggest that interventions based on the Mediterranean diet may prevent behavioural disturbances stemming from prenatal stress in a sex-specific way, perhaps independently of the diet actions on colonic tryptophan metabolism.

P3-F-720: Investigating spatial scrambling in amblyopia using letter discrimination with scrambled letters and convolutional neural networks

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Amblyopia is a disorder of the visual system, typically resulting from an impoverished input from one eye during early life. One defining feature of the disorder is spatial scrambling, which describes the neural deficit where the amblyopic eye's input is topologically disrupted. We aim to distinguish a possible scrambling at the input to the "oriented receptive field" stage against scrambling of that stage's output. To do this, we adopted a letter identification task and asked participants with amblyopia, control participants with normal healthy vision, and two convolutional neural networks trained on letters scrambled at input and output stages to perform the task. A performance comparison revealed the two scrambling approaches could be distinguished as the two networks adopted distinct strategies to doing the task. In the input scrambling condition, we extracted relative efficiency from normal and amblyopic data relative to the input-scrambling-trained network. Curiously, the amblyopic participants outperformed the controls when both were using their weak eye (amblyopic eye and non-dominant eye), suggesting that the processing of the amblyopic eye input is specifically resilient to the effects of our input scrambling. We also generated confusion matrices that characterized the mistakes participants made for the input scrambling condition and found amblyopic and normal eye conditions fell in distinct clusters via k-means clustering. Taken together, these findings suggest input processing of oriented receptive field differs in normal and amblyopic visual systems.

P3-F-721: The role of basolateral amydala neuronal ensembles in fear discrimination

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Activity in the basolateral amygdala (BLA) is crucial for the acquisition and expression of first-order Pavlovian fear. Such activity is restricted to a subset of neurons. Here, we wanted to examine the role of this subset of fear neurons in fear expression. We used a fear discrimination procedure in which one auditory cue (target; A->shock) but not another (control; B->nothing) was paired with mild aversive shock. Using fos-LacZ transgenic rats and the Daun02 inactivation technique we deleted the neuronal ensembles that were activated by the fear eliciting target cue and obtained a behavioural disruption of fear when rats were tested to the target. Deletion of the ensembles activated by the control cue left fear to the target intact. ß-galactosidase counts confirmed that the target activated fewer BLA neurons on

test in the deletion (daun02) compared to the control (vehicle) group. Further, we sought to investigate whether the deletion of the target cue memory would influence fear to another fear conditioned cue in a modality-dependent manner. Our data show that fear conditioned cues of the same modality activate the same neurons in the BLA. That is, daun02 inactivation of BLA neurons activated by one fear conditioned auditory cue resulted in a behavioural disruption of fear to the same as well as to the other cue. We consider these findings in terms of the role of BLA neuronal ensembles in partitioning fear memories.

P3-F-722: The ventral midline thalamus consolidates fear memory during sleep by mediating hippocampo-cortical coupling

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Sleep is essential for memory consolidation. Consistent with this role, sleep promotes bidirectional communication between the hippocampus, where memories are initially formed and the neocortex, where memories are stored for long-term retention. Precise synchronization between the two structures, a critical step in system consolidation, occurs through the coupling of field oscillations such as hippocampal sharp-wave ripples (SWRs, 100-300 Hz) and cortical slow oscillations (1-4 Hz). The ventral midline thalamus (VMT) extends bidirectional connections to the medial prefrontal cortex (mPFC) and hippocampus, giving it an ideal anatomical position for organizing hippocampo-prefrontal coupling. Using closed-loop optogenetic stimulation and in vivo intracellular recording in mice, here we show that phasic inhibition of the VMT during hippocampal SWRs promotes the consolidation of fear memory during NREM sleep. In vivo intracellular recordings demonstrate that hippocampal SWRs inhibit the VMT and trigger thalamic bursting and prefrontal depolarization. The result describe an inhibition-driven thalamic mechanism that organizes the transfer of hippocampal events to the thalamocortical system.

P3-F-723: Investigating the role of TNF-alpha in female rats' cocaine-seeking behaviour

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Tumor necrosis factor (TNF) is a pro-inflammatory cytokine secreted by glia in response to many stimuli, notably through the activation of their toll-like receptor 4 (TLR4). TNF promotes the internalization of AMPA receptors in striatal medium spiny neurons, which includes the nucleus accumbens, a key brain region in which signaling is altered following chronic cocaine use. Inducing the expression of TNF using a TLR4 agonist, monophosphoryl lipid A (MPLA), results in decreased behavioural sensitization to cocaine following repeated drug administration. Here we assessed the effects of MPLA treatment on progressive ratio responding for cocaine and cue-induced reinstatement of cocaine seeking in a rat cocaine self-administration model. Female Sprague-Dawley rats self-administered i.v. cocaine during 10 intermittent access sessions. Next, motivation for cocaine was assessed via a progressive ratio schedule of reinforcement before (baseline) and 24h following either an MPLA or saline injection. The rats then received 14 extinction sessions followed by a cue-induced reinstatement test. They received MPLA or saline 24h prior to this test. There was no effect of MPLA on progressive ratio responding, suggesting no effect on the motivation to take cocaine. Preliminary data suggest a trend towards suppression of cue-

induced reinstatement after MPLA treatment. These findings suggest that further studies are required to assess MPLA's role as a potential therapeutic for cocaine use disorder.

P3-F-724: Body representation and sound localization: A co-dependent process

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The influence of auditory cues on postural stability and body orientation has been widely studied. The interaction between sensorimotor and auditory cues is so strong that it has been suggested that spatial representation can be based solely on this interaction, in the absence of visual information. In contrast to the very large body of findings confirming the influence of auditory cues on body perception and movement-related activity, the influence of body representation on spatial hearing has never been examined. Here, we use a classic disorientation task to assess whether a change in the orientation of the body in space could lead to a significant illusory shift in the localization of a sound source. Participants were asked to locate a fixed sound sequence before and after performing the Fukuda-Unterberger stepping test, a task known to alter the spatial orientation of the body without awareness that a shift has occurred. While all participants were initially able to locate the sound source with great precision, they all made substantial errors in judging the position of the same sound source following the body-orientation altering task. These results demonstrate that a change in body orientation can have a significant impact on the auditory processes underlying sound localization. The illusory localization errors not only confirms the strong connection between the two sensory domains, but also raises questions about the relative importance of hearing in determining spatial position.

P3-F-725: Hyperlipidemia promotes blood brain barrier loss and heightened inflammation in the hippocampus: mechanisms of vascular dementia

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Vascular cognitive impairment (VCI) is a form of dementia, caused by vascular dysfunction and/or cerebrovascular disease (CBVD). Some associated risk factors are elevated cholesterol, hypertension and a sedentary lifestyle. The pathogenesis of VCI includes changes in the cerebrovascular function, accumulation of atherosclerotic plaques within large and small arteries, blood-brain barrier (BBB) structure and function breakdown and altered cerebral blood flow (CBF). However, little is known about diseases within the cerebrovasculature and specifically about the cause of VCI. This research objective is to identify novel mechanisms that promote inflammation, BBB dysfunction and its association with VCI in a hyperlipidemia context. For this, we work with two mice models: LDL receptor (Ldlr) and Lrp1 double KO mice (Lrp/Ldlr-/-) and apolipoprotein E KO mice (Apoe-/-). The Lrp/Ldlr-/- mice had significantly elevated plasma cholesterol and advanced aortic atherosclerosis lesions, after 8 weeks feed with Western diet (WD, PMID 12690199). A reduced CBF (as measured by MRI) and impaired cognitive function (as measured by the Novel Object Recognition test; NOR and Morris Water Maze; MWM). We observe ECs CD31+ loss and increased GFAP+ cells indicating astrogliosis in the hippocampus. In Apoe-/-

mice, with less severe hyperlipidemia and atherosclerotic lesions, we also observe cognitive impairment but only after 24 weeks with WD (NOR and MWM). Additional analyses, including BBB integrity, astrocyte activation, cholesterol accumulation within ECs of the microvasculature and transcriptional analyses of inflammatory pathways are currently being analyzed. Together, these data will determine how the interplay between excessive cholesterol and inflammation drives VCI pathogenesis.

P3-F-726: Functional Brain Networks for Egocentric and Allocentric Memory-guided Reaching.

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The location of a remembered reach target can be encoded in egocentric and/or allocentric reference frames. While the differences in the cortical activation of these two representations have previously been identified (Chen et al., 2014; Neggers et al., 2006), differences in the functional organization of brain networks have not been described. It is expected that the size and connectivity of those functional brain networks will differ. Here, we performed a secondary analysis of an event-related fMRI task (Chen et al., 2014), to distinguish human brain networks involved in these two forms of representation. The paradigm consisted of three tasks with identical stimulus display but different instructions: egocentric reach (remember absolute target location), allocentric reach (remember target location relative to a visual landmark), and a non-spatial control, color report (report color of target). The properties of brain networks involved were analyzed using graph theory. The allocentric task demonstrated less hubness, lower clustering and increased global efficiency. This connectivity pattern is indicative of increased overall connectivity - between dorsal and ventral visuomotor regions. An analysis of the modularity revealed three important brain modules, two dorsal and one ventral. The allocentric task showed higher modularity in the anterior dorsal brain module, whereas the egocentric task showed increased modularity in the posterior dorsal brain module. Connectivity between both dorsal modules and the ventral brain module was highest in the allocentric task. Thus, we show differences in functional connectivity of dorsal visual stream for the allocentric task. More anterior brain regions, including frontal areas could be more important for a rule-based spatial coding.

P3-F-727: Examining working memory capacity in freely moving marmosets

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Working memory (WM) describes the maintenance and manipulation of information relevant to goal-directed behaviour for short time intervals. There are limits on the number of memoranda that can be reliably maintained in WM. Interest in marmosets as a WM model has recently burgeoned, and their lissencephalic smooth cortex renders them a particularly tractable system for studying layer-specific neurophysiology. Marmosets have been shown to perform simple working memory tasks such as delay match-to-sample or match-to-location. However, WM capacity in marmosets is less studied. Studies have shown that neuronal WM activity is progressively degraded with increasing load in the macaque prefrontal cortex. However, how activity in different prefrontal cortical layers is modulated by WM load is not known. We developed a freely moving touchscreen system to train marmosets in an iterative delayed non-match-to-position span task to investigate this. Subjects indicate the position of the novel

visual stimulus that was not presented on previous iterations of stimulus presentation, with delay periods wherein the locations of previously presented stimuli must be maintained in WM. We trained five animals to perform this task and assessed their performance by computing their position span length across training. Our results show that marmosets can learn to perform a WM load task with improved span length with progressive training. We implanted marmosets with a multishank volume electrode array and are using wireless recordings to assess the layer-specific contributions to WM capacity.

P3-F-728: More evidence that ensemble music training influences childrens neurobehavioral correlates of response inhibition during executive attention tasks.

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The ability to self-regulate has been associated with school-readiness and academic achievement. A previous body of research has indicated that young children receiving music instruction perform significantly better on self-regulation tasks. The current study assessed the neurocognitive correlates of response inhibition using event-related potentials (ERPs) as children between the ages of 9-12 years with and without training in a social music program, OrKidstra, completed an auditory Go/NoGo task involving pure tones at 1100Hz and 2000Hz. Preliminary findings indicate that participating in the OrKidstra program decreases children's reaction times to Go stimuli and increases the early brain's response to this tone within individuals (2000Hz vs. 1100Hz in the same children) and between groups (OrKidstra children vs. comparison children). Children also completed the Peabody Picture Vocabulary Test, Fourth Edition (PPVT-IV) to allow us to determine the influence of music learning on verbal comprehension. Family demographics and wellbeing were collected through questionnaires completed by the child's parent/guardian. Findings from our research may have implications for music training interventions and music training implementation in the school setting, especially as applied to socioeconomically disadvantaged children.

P3-F-729: Examining hippocampal task-relevant coding in rats freely moving in a virtual-reality Dome apparatus

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The hippocampal formation is thought to encode the cognitive map, a neural representation of the spatial environment of an animal. However, recent studies indicate that hippocampal neurons can additionally represent non-spatial cues that are informative of the animal's behavioural task. We investigate hippocampal encoding of task-relevant cues in freely moving animals using a virtual-reality Dome apparatus. In the Dome, rats run freely on a circular track while being surrounded by projected visual cues and listening to sound frequency cues. They are trained to request reward through nose-pokes at specific locations within the task-relevant auditory reference frame, which moves with respect to the task-irrelevant, stationary visual frame according to a predetermined experimental gain value. Behavioural data shows that rats are able to perform this task with high accuracy. We are recording population activity in hippocampal CA1 in well-trained rats, and predict that place cells will encode

locations in both task-relevant and task-irrelevant reference frames, and a subset of cells will perform purely task-relevant coding. We will test these hypotheses by quantifying spatial information scores of CA1 population activity in the circular task-relevant and task-irrelevant frames, and a conjunctive toroidal frame. We will also independently quantify the topology of the neural representation using geometric deep learning techniques and compare it with the topology of the task.

P3-F-730: Pathophysiology of retrosplenial cortex associated with cognitive impairment in mouse models of schizophrenia

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Schizophrenia (SCZ) is a severe, chronic illness that manifests with psychopathology 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 node of the DMN, retrospelnial cortex (RSC) is involved with a range of cognitive functions including memory and spatial navigation. While regional dysfunction in RSC has been described, the cellular and network level changes and the mechanisms of this dysfunction has not been well defined. Here male and female C57/BL6 wild-type animals were treated with acute or chronic (14 days) treatment with ketamine (30mg/kg, or vehicle control). Our data revealed that acute and chronic ketamine regimens impaired spatial and non-spatial cognitive ability in a sex-dependent manner. To relate impairments to alterations in neuronal and microglial physiology, in vivo two-photon as well as confocal microscopy were employed. Imaging data obtained from acute and chronic ketamine treated Thy1-GcAMP6s:PV-tdTomato transgenic mice showed sex-dependent alterations in neuronal spiking of parvalbumin (PV) positive inhibitory interneurons and non-PV neurons in the local RSC network. We hypothesize that network disruptions due to altered PV activity may result from degradation of perineuronal nets that ensheath these inhibitory interneurons by activated microglia. Notably, preliminary data shows greater activation of microglial cells in RSC following chronic treatment. Future experiments will further define neuronal and inhibitory network activity alterations associated chronic ketamine and the role of microglia in driving this network dysfunction.

P3-F-731: Aberrant explore-exploit decision making in a mouse model of autism spectrum disorder

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Autism Spectrum Disorders (ASD) are characterized by cognitive deficits, repetitive behaviors and difficulty navigating social and novel settings. Despite a growing understanding of underlying mechanisms, the common etiology of these seemingly unrelated traits remains unclear. Recently, promising theories of ASD proposed that aberrant processing of perceptual uncertainty is a central cause of ASD symptomology. However, it remains unclear whether these deficits extend to reward processing, and how this may impact decision making circuitry. We developed a probabilistic reversal learning paradigm amenable to in vivo two photon imaging and behavioral modeling, wherein head-fixed mice learn evolving, probabilistic cue-action-reward associations. We found that mice with a syntenic deletion

of the 16p11.2 locus (a mouse model of ASD) learned the task at the same rate as controls. However, 16p11.2 /- mice collected more rewards after learning, and less rewards after a rule reversal. We fit a reinforcement learning model to choice and reward data, which revealed that these differences were attributable to a single parameter related to the exploration-exploitation trade-off. 16p11.2 /- mice prioritized exploitation of high-value choices: this maximized rewards under stable conditions, but hindered adaptation after a reversal. Future experiments will use in vivo calcium imaging to investigate reward uncertainty representations in prefrontal networks of 16p11.2 /- mice. We intuit that a better understanding of uncertainty processing in the autistic brain may lead to improved therapies.

P3-F-732: Social isolation exacerbates the cognitive decline observed in aging through a mechanism that involves a decrease in autophagy and changes in cell cycle

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Introduction: Cognitive decline often occurs during aging. In addition, social isolation, often associated with aging, can also lead to cognitive decline. Yet, it is not known whether defects in cognition due to aging are compounded by social isolation. It has been shown that social isolation causes deficits in autophagy. Therefore, we hypothesize that cognitive decline will become more pronounced if we inhibit autophagy in aged mice through social isolation. Methods: To address this, we treated mice with D(+)Galactose to induce aging and subjected them to long-term post-weaned social isolation. Then, we assessed cognitive function with Y-maze, Morris water maze (MWM), and passive avoidance tests (PATs). We used western blot to determine protein expression levels in hippocampal samples. Results: Both aging and social isolation impaired cognitive function; however, the impairment was more severe when aging was combined with social isolation. Moreover, in both aged and socially isolated mice, we found a 2-fold significant reduction in the synaptic protein, PSD95, and in dendritic spines density. The Autophagy substrate, p62, was upregulated whereas Beclin1 decreased. Cell cycle markers (p16, cyclin D1, PCNA) increased. Discussion and Conclusion: Our results show that social isolation exacerbates the cognitive decline observed in aging through a mechanism that involves a decrease in autophagy and changes in the cell cycle. The close association between isolation and aging in humans is very real. The results of this study could be explored for possible interventions and therapy.

P3-F-733: Time-dependent inhibition of Rac1 in the VTA enhances a consolidated aversive memory as a potential active forgetting mechanism

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INTRODUCTION: Active forgetting (AF) of consolidated appetitive memories in the rat involves a dopamine-dependent mechanism in the hippocampus and the ventral tegmental area (VTA). Yet, the molecular mechanisms underlying the AF of memories, particularly consolidated aversive memories, are poorly understood. There is evidence that GTPase Rac1 has an active role in the forgetting of some types of memories. Therefore, we asked whether Rac1 mediates AF of an aversive fear-related memory.

METHODS: We trained male rats in the step-down inhibitory avoidance task and tested them at 1 h, 24 h, 7 d and 14 d after training. In addition, the animals were injected into the VTA, the hippocampus or the amygdala with either vehicle or the Rac1 inhibitor, NSC23766, at various times. RESULTS: Post-training injection of the Rac1 inhibitor into the VTA enhanced inhibitory avoidance memory at 24 h, 7 d and 14 d. while the non-consolidated memory tested at 1 h was not altered. Moreover, no effect was observed when the injection was made into the VTA after test or into the hippocampus or the amygdala. Surprisingly, the injection of the Rac1 inhibitor into the VTA at 12 h after training reduced memory expression at 24 h, suggesting that this protein could have different effects on memory depending on the time after acquisition. DISCUSSION: Taken together, our results suggest that Rac1 in the VTA contributes to an AF mechanism for one type of consolidated aversive memory. Moreover, this effect seems to be region- and time-specific, meaning that this process could be accurately regulated.

P3-F-734: Studies of memory, perceptual and attentional processes in healthy and brain injured subjects at the University Hospital of Oujda Morocco: Case of head trauma

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Abstract Head trauma is an important public health problem. Most epidemiological studies show that the incidence is highly variable depending on the country, the global prevalence of which is high. In Africa, particularly in Morocco; in this work we studied memory, attention and visual disorders in patients with traumatic brain injury. Method: In order to evaluate the cognitive processes (attention, executive functions), the study is carried out in the Neurosurgery Department of the University Hospital Center of Oujda (Morocco). It includes 40 people from the Moroccan population, of whom 20 are head trauma subjects, 20 control subjects, with an average age of 34.38 standard deviation of 15.79, an extreme age of 15 to 68 years. We used an exploitation sheet, the D2R test and the Rey's Complex Figure (RCF-A) version computerized by the ELIAN software. Result: The result obtained shows that the control subjects have good cognitive processes than the traumatized patients. Moreover, there is a significant difference between the head traumatized group and the control group. There is a significant disparity between the two groups, both in terms of the scores of the two D2R and RCF-A tests and in terms of the types (strategies) of RCF-A achievements. Conclusion: From this fact we can conclude that our patients have difficulty concentrating and paying attention, as well as they suffer from perceptual and memory impairment.

P3-F-735: Environmental conditions of recognition memory testing induce neurovascular changes in the hippocampus in a sex-specific manner in mice

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Experiences are linked to emotions impacting memory consolidation and associated brain neuronal circuits. Posttraumatic stress disorder is an example of strong negative emotions affecting memory processes by flashbacks of past traumas. Stress-related memory deficits are also observed in major depressive disorder (MDD). We recently highlighted that sex-specific blood-brain barrier (BBB)

alterations underlie stress responses in mice and human depression. However, little is known about the relationship between emotional valence, memory encoding and BBB function. Here, we investigated the effects of novel object recognition (NOR) test, an experience considered of neutral emotional valence, on BBB properties in dorsal vs ventral hippocampus in the context of various environmental conditions (arena size, handling, age). The hippocampus is a brain area central for learning and memory processes with the dorsal and ventral subregions being associated with working memory vs reference memory retrieval, respectively. Expression of genes related to BBB integrity are altered in line with learning and memory processes in a region- and sex-specific manner. We observed correlations between poor learning, anxiety, stress-induced corticosterone release and changes in BBB-associated gene expression. Comparison of BBB transcriptomes between sexes also revealed profound differences at baseline in both ventral and dorsal hippocampus. Finally, we identified circulating vascular biomarkers, such as sE-selectin and Mmp-9, altered following NOR exposure supporting that recognition memory formation has an impact on the neurovasculature. Although deemed as a neutral valence test, NOR experimental conditions impact performance, highlighting the need to minimize anxiety when performing this test.

P3-F-736: Tools in haptic exploration with early loss of vision: Using deep learning to Investigate complex behavioral correlates of novel neurocognitive processes and underlying plasticity.

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During development, specialized regions in the brain are primed by sensory and perceptual input to be preferentially recruited for specific tasks involving language, motor control, and object recognition. When the ability to perform these tasks is disrupted early in the life span such as in the case of congenital blindness, a possible occurrence is the remapping of the specialization of these regions to support other cognitive functions (compensatory plasticity). In our study, we explore potential neurocognitive remapping in Congenitally Totally Blind (CTB) and Sight but Visually Impaired (SVI) children performing a haptic identification task with raised-line schematic images (haptic pictures). We employ deep learning to quantify perceptual attention and stochastic haptic exploration by tracking finger movements in recorded videos. This sensory and kinematic data reveals movement clusters that offer insight into different machine learning tools which may be leveraged to explore, discover and compare novel complex behavioural correlates of neurocognitive processes. Furthermore, said exploration and analysis implies potential compensatory plasticity associated with performance differences or equivalences between and within groups.

P3-F-737: Estrogen Receptors in the Medial Amygdala: Interactions with Oxytocin Signalling on Social Recognition

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Estrogen Receptors in the Medial Amygdala: Interactions with Oxytocin Signalling on Social Recognition Dante Cantini | dcantini@uoguelph.ca Estrogens act via three main receptors (ERα, ERβ, GPER) distributed throughout the central nervous system. These estrogen receptors are highly expressed in areas of the social brain and are extensively implicated in rapid effects on social recognition memory.

Rapid effects are defined as receptor-mediated signalling that occurs too quickly to be associated with immediate gene transcription. In females, estrogen binding in the medial amygdala triggers rapid effects that facilitate social recognition. Oxytocin signalling within the medial amygdala must be present for estrogenic rapid effects on social recognition to occur. This study aims to determine which estrogen receptors within the medial amygdala are involved in the interplay with oxytocin that results in rapid facilitation of social recognition. Female mice had the respective estrogen receptor agonist bilaterally infused into the medial amygdala with an oxytocin receptor antagonist. A social recognition paradigm designed to measure rapid effects was conducted to assess social recognition performance. Microdialysis and ELISA will be conducted to determine extracellular oxytocin within the medial amygdala following agonist infusions. We predict that the activation of one or more of the estrogen receptors leads to a signalling cascade resulting in the synaptic release of oxytocin and subsequent facilitation of social recognition. Determining the mechanisms of estrogen receptors and their functional interactions in the brain is essential to understanding the biological underpinnings of normal social behaviour.

P3-F-738: The cognitive aspects of perception and what they tell us about the future of computation

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Whether or not the brain is a kind of computer, and the essence of its representations remains highly controversial (Churchland et al., 2017). Perhaps it was Alan Turing (1950) who first had human minds buzzing with questions and debates about computational machinery and whether the brain could be characterized in terms of some procedure of mathematical functions. Perception is one of the computation and deep learning areas explored since there are still large gaps in our understanding of perceptual processes (Tsodyks and Gilber, 2004). Specifically, computation tasks for imagination provide a better understanding of perception and its cognitive connections (Weber et al., 2018). Mapping what is required for perceptual computation onto what we know about human perception can give insight into both the perceptual and computational debate. Furthermore, deep learning research assists in supporting the connection between human experience, imagery, and perception. Through comprehensive review, this research focusses on bridging the gap between computation and human perception to uncover perceptual properties and show the translational usefulness of computation to brain research. Through the combined efforts of human and computational research, it is possible to study not one, but many cognitive aspects of perception including experience, attention, imagery, and memory. We found that computational modelling and deep learning can not only mimic a humans' perception but provide insight into the integrated factors necessary for human perception.

P3-F-739: Sharp wave ripples in the human hippocampus during associative learning and virtual navigation.

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Hippocampal sharp-wave ripples (SWRs) are manifestations of rapid bursts of neuronal activity generated by the dendrites of CA1 pyramidal cells in mammals. SWRs play an essential role in memory

formation and navigation. However, SWR rates and their distributions during associative learning tasks and navigation have yet to be compared. Using the context-associative memory paradigm, we attempt to find the link between the learning and SWR rates. We hypothesize that learning will increase the likelihood of hippocampal SWRs relative to spatial navigation. We designed a paradigm composed of a maze and two Y branches on either side in a virtual environment. There are two objects at the end of the maze that the player must reach after textures appear on the walls. There is an association between the colours and appeared context, determining correct and incorrect responses. At Western University Hospital, epilepsy patients implanted with macroelectrodes (depth electrodes) were asked to participate in playing our game. We detected SWRs in the signals using our customized algorithm. Seven of the ten participants learned the game, and three did not. In those who learned the task, hippocampal SWR rates (events per second) were statistically significantly higher during the game rather than resting state. Two specific increases were detected during the game. However, they occurred at a similar frequency during the associative learning period and during navigation. SWR rates did not change (compared to the resting) in those who did not learn the game.

P3-F-742: Trans-saccadic information carry-over in visual search

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Saccadic eye movements bring parts of the visual scene onto the fovea. Each saccade is generally followed by a ~125-600 ms period of fixation, during which the selected region is analyzed and the next saccade target is chosen. Previous studies have identified situations (pop-out search, double-step search, anti-saccade tasks) where fixation periods much shorter than 125 ms can be found, indicating that the saccade after this short fixation is influenced by visual information obtained during a preceding fixation. In these previous studies, the task goal was extremely salient, and the short fixations were followed by saccades towards this salient task goal. Here, we explore whether short-latency saccades can also be found during more naturalistic, free-viewing visual search. Healthy humans (N = 13) searched for a T-shaped target among seven distractors. Subjects had to identify a brief (~12 ms) left- or rightward extension of the horizontal bar of the T, and in order to do this, they naturally searched for the T and foveated it, making predominantly one (36%) or two (43%) saccades. About 40% of the second saccades had latencies less than 125 ms. These saccades were not just small corrective saccades, and they were more likely to foveate the search target than second saccades preceded by longer fixation periods. First saccades, however, showed the usual speed-accuracy tradeoff where slower saccades were more likely to be target-directed. These results will guide our modeling of trans-saccadic information transfer during free-viewing visual search.

P3-F-744: Acute D-serine rapidly rescues deficits in pattern separation following high fat high sugar diet consumption

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Low adherence to lifestyle changes because of the accessibility and inexpensiveness of fatty and sugary foods have contributed to the increased prevalence of cognitive decline in Canada. Consequently, studies

have found that noticing subtle differences in changes to objects and locations - a memory process known as pattern separation - becomes increasingly difficult with the overconsumption of high-fatty and/or high-sugary (HFHS) foods. The objective of this study was to examine if a readily available supplement, D-serine, can rescue pattern separation in mice fed an HFHS diet. Male and female C57Bl6 mice were fed either an HFHS diet (n=31) or a control diet (n=28) for 28 days. Memory was then tested on three versions of the spontaneous location recognition (SLR) task. Two hours prior to completing the task, mice were randomly assigned to treatment with D-serine or saline-injected (intraperitoneal). SLR assesses pattern separation by measuring the extent that mice can discriminate between identical objects manipulated in the similarity of location between them: dissimilar (ds-SLR), similar (s-SLR), or extra similar (xs-SLR). HFHS diet-induced significant adipose and liver weight gain in mice. When demands on pattern separation were high, HFHS diet led to impairments in memory under s-SLR conditions compared to control-fed mice. D-serine rescued performance in HFHS-fed mice tested on d-SLR and s-SLR while also enhancing pattern separation ability in xs-SLR, irrespective of diet, in both males and females. Our results indicate that acute systemic administration of D-serine can recover pattern separation in HFHS-fed mice. Overall, D-serine can offer fast enhancements of cognition following the consumption of HFHS diets.

P3-F-745: Adolescent social isolation alters affective and social behaviour across the transition to motherhood in adult female mice

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Adolescence is a critical period marked by significant neural and behavioural development in social and emotional domains. Adolescent social stress can lead to lasting behavioural alterations and increased risk for psychopathologies in adulthood. In adult females, the transition to motherhood is another period of substantial emotional and social adaptations and increased risk for psychiatric disorders. Here, we characterized the effects of adolescent social isolation stress on adult female behaviour across the perinatal transition. Female mice were socially isolated (isolation-reared) or group-housed (group-reared) from postnatal days 21-42. In adulthood, mice were assessed on tests for affective and social behaviour prior pregnancy and in the postpartum period. Isolation-reared mice displayed reduced sociability toward age-matched female conspecifics across the perinatal transition, and increased latency to retrieve pups in the postpartum period, indicative of reduced maternal motivation. Interestingly, isolation-reared mice exhibited increased exploratory behaviour in the open field test, reduced immobility in the forced swim test and lower latency to retrieve pups in a challenging version of the test, indicating potential alterations in stress responsivity. These data suggest that adolescent social isolation may dynamically shape adult female affective and social behaviour depending on the degree of acute stress or challenge.

P3-F-746: A comprehensive neuroanatomical study of the reptilian Nile crocodile (Crocodylus niloticus) posterior telencephalon

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Crocodilians, a resilient reptilian taxonomic grouping, share a very close phylogenetic evolutionary relationship to birds. Moreover, crocodiles can perform complex behaviours comparable to those of birds. A specific avian forebrain region, the nidopallium caudolaterale (NCL), is thought to be involved in cognition. However, the reptilian forebrain region directly implicated in cognition has not been determined definitively. A comprehensive study of the lizard forebrain suggests that the posterior dorsal ventricular ridge (PDVR), a unique region of the reptile telencephalon, might be the functional equivalent of the NCL. Therefore, we aimed to determine the divisions of the PDVR and its associated structures within the crocodilian posterior telencephalon. Methods: The brains of 4 juvenile Nile crocodiles were stained for nissl, myelin, parvalbumin, calbindin, calretinin and tyrosine hydroxylase, and analysed with a standard fluorescent microscope. We used stereology to quantify the neuroarchitectural boundaries, extrapolating differences in cell density profiles and cell volumes of posterior telencephalon. Results: The results reveal five different subdivisions of the posterior telencephalon, namely: the medial, intermediate and lateral portions of the PDVR, the periamygdaloid cortex and the nucleus sphericus. Discussion: Our results define six neuroanatomical regions of the crocodilian posterior telencephalon, including a nucleus sphericus, which had previously been thought to be absent in crocodilians.

P3-F-747: Towards real-world cognitive neuroscience applications: a virtual reality platform to predict operator performance during robotic operations

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Cognitive neuroscience has the potential to improve human safety and performance, but attempts to transfer knowledge of cognition and its physiological correlates from laboratory studies to real-world applications have had limited success. We are exploring applications of intermediate, immersive test platforms that can be used to create naturalistic study environments, while maintaining experimental control in the context of safety-critical operations (e.g., in transportation, mining, exploration, and controlling robotics). Artificial-intelligence (AI)-controlled robots are increasingly being used in self-organizing fleets; in transportation, industrial, commercial, and emergency response applications. However, human cognitive capacities are challenged by increasingly complex and opaque AI systems, with consequences to safety and mission success when they are exceeded. Cognitive workload (CW) (i.e., mental resources required to perform a task) can be used to predict and improve operator performance. Cognitive workload is typically studied with neurocognitive tests in a controlled setting, or with behavioral rating scales in safety-critical real-world environments. We will present our research program in which virtual reality (VR) serves as an intermediate platform between the laboratory task and naturalistic studies. Specifically, we are developing immersive and engaging VR realistic missions (e.g., drone fleet driving), while maintaining control over task parameters so as to enable rigorous neurocognitive assessment.

P3-F-748: The neurobiological impact of rodent transportation: A meta-analysis and systematic review

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There are well established links between excessive commuting and negative health consequences for humans. From a physiological perspective, commuting increases BMI and blood pressure while decreasing cardiorespiratory fitness and physical activity. From a psychological perspective, commuting increases sleep disorders and stress, while impairing cognitive processes. These negative consequences are also observed in animals. In addition to direct adverse effects on the wellbeing of research animals, the impact of transportation compromises the scientific accuracy of our models. The intensive development, use and sharing of diverse rodent models in scientific studies requires ongoing and at times, global shipment of many animals. This transportation heavily impacts rodent physiology, including cardiovascular, endocrine, immune, and digestive systems. These all lead to changes in their neurophysiology and ultimately, behavior. If not accounted for, these practices introduce confounding variables with the potential to conflate most studies. The objective of this study is to provide a systematic review summarizing the research from the last 20 years in this area. Specifically, the effects of transportation on rodent physiology and behavior are reviewed. Through meta-analysis, these changes are quantified and analyzed. Lastly, some recommendations for optimizing rodent transportation are discussed to reduce the adverse effects of shipping and provide a means for mitigating this key but underappreciated aspect of contemporary animal research.

P3-G-749: Smart Priority Model for Urban governance applications Based on Brian Neural System

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The brain neural system as a highly complex and complete synaptic system has been one of the best data management guides to apply in various scientific fields. In this article, Local Cooperation System (LCS), with a goal of citizens' request management in the Smart City, is suggested based on a synaptic integration system. Prioritizing Citizen Request (CR) is an important element of their identification and evaluation which it could be created an intelligent system to prioritize requests by applying LCS features. Accordingly, it is very difficult to respond to all requests. Therefore, this act causes of decreasing level of citizens' satisfaction. Firstly, the proposed system, with the help of CRNs, prioritizes and manages these CRs. Secondly, if these CRs are not considered due to the low priority of the CRs, the CR creator will be satisfied with the state due to the democratic nature of the review process. The LCS could be as a core of many urban applications such as Citizen Relationship Management and CR mobile Applications. The LCS could enhance good urban governance, solve city problems and categorize of data in order to achieving more citizens' cooperation, more responsibility of governance, consensus-oriented decision making and management of data. Keywords: Smart City; Governance Mobile Application; Brain Neural System; Local Cooperation System (LCS); Smart Request (SR)

P3-G-750: Stem Cell-Derived 3D Co-culture 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, which surveil their surroundings and can orchestrate potent responses to brain damage and immune stimuli. Unlike neurons or glial cells, microglia have a unique developmental origin outside the brain. 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 recapitulate this developmental trajectory ex vivo, and study the coordinated development of brain and microglia, we have established 3D co-cultures between human pluripotent stem cell-derived microglia and neuro-glial cells. Changes in microglia morphology, behavior and transcriptomes were observed. We then engineered distinct brain environment mimicking either different brain regions or different brain cell types and have been testing their effects on resident microglia. In addition, we are also examining the effects of microglia re-addition and depletion on 3D co-culture. 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-G-751: Imaging membrane potential in a fast and temporally and spatially very precise way in large 3D volumes with real time motion correction

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Access to large scale but subcellular resolution voltage signal data in the awake behaving animal was so far very limited because of technical constraints. Understanding the computation in the three dimensional neural networks is virtually impossible without that sort of data. Here we show how it is possible with the groundbreaking genuinely three dimensional acousto-optical multiphoton microscopy to obtain temporally and spatially extremely precise (imaging) data that reveal network-level processes based on subcellular resolution recording. We recorded membrane potential data along with calcium signal from the visual cortex of awake behaving mice and also used (in different subjects) optogenetic manipulation simultaneously in 3D to modulate activity. To avoid motion artifacts and maximize recording speed over a large volume we used real time motion correction based on the acousto-optical principles, special hardware and algorythms. In our presentation we highlight processes that are revealed with these groundbreaking methods using the latest available voltage sensitive indicators.

P3-G-752: Effects of peripheral functional electrical stimulation in combination with low intensity focused ultrasound on upper extremity fine motor function

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Acquired neurological conditions may result in diffuse and widespread cortical activation changes associated with loss of movement of the limbs. Recovery is slow and often limited. The objective of this study was to examine the feasibility and effects of combining theta burst transcranial ultrasound (tbFUS) to left motor cortex with functional electrical stimulation (FES) for grip training in healthy subjects. We

hypothesized that tbFUS combined with FES will result in an increase in motor evoked potential (MEP) amplitude and an improved performance on the nine hole peg test (NHPT). Positive findings have the potential to improve functional outcomes and reduce treatment duration. Ten healthy participants underwent 2 study visits. Each study visit consisted of real or sham tbTUS immediately followed by 30 mins of FES. The Real tbFUS consisted of an 80s train of 20ms ultrasound bursts, repeated every 200ms. Sham tbFUS consisted of the same paradigm with the ultrasound transducer flipped so that the active surface pointed away from the scalp. This was followed by FES of the right hand muscles triggered in congruence with voluntary effort of the participant during execution of functional tasks. NHPT scores and MEP data using transcranial magnetic stimulation were collected from the abductor pollicis brevis, first dorsal interossei (FDI) and abductor digiti minimi muscles at various time points during each visit. Preliminary data shows that real tbFUS + FES results in intracortical inhibition as seen by decreased MEP amplitude immediately post-completion of the two interventions with a recovery in amplitude 30 mins post-completion.

P3-G-753: Breaking the mold: deep learning model for suicide ideation detection in social media

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Intro: In this interconnected world, digital tools have the potential to improve patient's experience and health providers' response-ability. Aim: The present research is a three-study project on the development of an early-stage deep-learning model to improve health system capacity for targeting and real-time mental health surveillance and prevention of suicide and psychiatric stressors. Methods: Study 1 uses data science and machine learning to build a corpus for model training. Study 2 reports on developing the deep learning model and assessing its incremental value over simpler machine learning. For further validation, Study 3 integrates the model to predict suicide ideation and intention from risk factors over social media posts (tweets). Results: Compared to traditional retroactive methods, the proposed model provides enhanced visibility to suicide and suicide ideation. Specifically, our results show that depression and behavioral intent of suicide are predictors of suicide ideation for tweets expressing thinking about suicide or planning suicide only. Hurt/anger, psychological disorder, and behavioral intent are predictors of suicide when all tweets about suicide, including those referring to suicide in a figurative way, are included. Conclusion: The research disrupts traditional systems, challenging the role of marketing in bettering public health and healthcare through the assistance of an informative road map for cost-effective, consumer (patient)-centered innovation. It particularly shows how social media platforms can be a real-time surveillance tool for suicide prevention and interventions.

P3-G-754: Simultaneous fluorophore discrimination and resolution improvement of super-resolution images using fluorescence lifetime

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To study the interactions between neuronal proteins with fluorescence microscopy, simultaneous observation of multiple biological markers is required. SPLIT-STED, an approach exploiting the analysis of fluorescence lifetime was developed to improve the spatial resolution of STimulated Emission Depletion microscopy [1]. We developed an analysis approach using the law of linear combination of components in phasor space [2] to multiplex SPLIT-STED and apply it to separate two spectrally indistinguishable fluorophores per imaging channel. We quantify and characterize the performance of our algorithm on simulated images constructed from real single-staining images. This allows us to perform simultaneous resolution improvement and colocalization analysis of multiple protein species in live and fixed neuronal cultures. In fixed samples we imaged synaptic protein pairs and could visualize synaptic nanodomains. We also discriminate cytoskeletal proteins from synaptic proteins despite a large percentage of the images' pixels containing mixtures of species. When applied to STED nanoscopy in living neurons, the multicolor SPLIT-STED approach allows the characterisation of neuronal protein organization at the nanoscale with reduced light exposure and photobleaching effects. Multicolor SPLIT-STED opens the door to future experiments studying dynamic neuronal protein interactions at the nanoscale. [1]G. Tortarolo et al., Nanoscale. 11, 1754-1761 (2019). [2]A. Vallmitjana et al., Methods Appl. Fluoresc. 8, 035001 (2020)

P3-G-755: Tissue engineered nerve conduit for peripheral nerve repair in a rabbit model

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Peripheral nerve repair is a clinical challenge. Nerve tube (NT) made of biomaterials can be used to guide axonal migration of the sectioned nerve but faces several limitations. Our goal is to produce a viable NT using the patient's own cells and pre-seeded it with endothelial (ECs) to allow a faster recovery. A nerve tube containing a pre-established capillary network, which can connect quickly to the host's microvasculature, should be a promising option to repair large nerve defects (>3cm). NT are made of human fibroblast sheets seeded with ECs and rolled to form a tubular structure. NT were implanted to repair a 4 cm fibular nerve defect in immunosuppressed New Zealand rabbit. Electrodiagnostic testing and functional assessment were performed over 36 weeks. The nerve conduction was evaluated monthly under light anesthesia. The Toe Spread Index (TSI) was used to monitor the functional outcome. Nerve conduction analysis in the tibialis anterior muscle showed that nerve recovery began around the 18th week. The electromyogram showed a resting electrical activity return with multiple polyphasic activities (I.e., reinnervation in progress) around the 24th week. After 36 weeks, an improvement of the TSI showed a partial motor function recovery in rabbit with autograft ($p<0.05$) that was also observed in the NT group but as a non-significant trend. Our approach to develop a prevascularized living autologous NT promoting a rapid vascularization of the graft is essential to support axonal migration over long distances and could be a promising new clinical tool to repair large lesions.

P3-G-756: The Omniroute maze: a novel apparatus enabling dynamically configurable routes and visual-cues

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We have developed a novel physical maze that enables highly flexible experimental control comparable to that afforded by virtual reality (VR) systems but in the context of unconstrained real-world rodent behaviour. The maze is composed of a 2.1 x 2.1 m platform with 308 independently movable wall segments that can be programmatically reconfigured to generate unique routes. The use of octagonal geometry accommodates both orthogonal and diagonal path trajectories. Four projectors arrayed around the perimeter of the maze can display distinct visual cues on any subset of raised walls, while an additional 4 projectors can display distal cues on the surrounding curtains. The system also incorporates high-speed 3D tracking of rat position and orientation for closed-loop control of the available paths based on real-time behaviour. Additionally, we developed a custom reward delivery system to provide food-based reinforcement anywhere in the maze. We will use the maze apparatus to electrophysiologically investigate the neural correlates of increasing task complexity in the cognitive map of rodents. Human participants will engage in a comparable task in a VR maze, allowing us to investigate the behavioural and neural impact of neurodegenerative dementias on navigation through a cross-species approach. The maze was designed from the ground up to use affordable, non-proprietary, open-source hardware and software, with an eye toward accessible fabrication and assembly that will aid replicability by other investigators.

P3-G-757: Multiplex analysis of disease associated PTEN variants using mass cytometry

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Autism spectrum disorder (ASD) is the most common genetic neurodevelopmental disorder, yet no effective treatment options are available. Genome wide sequencing has implicated 100s of genes in the development of ASD. One gene that has been well established to have strong links to ASD is the tumor suppressor PTEN. The most common disease associated PTEN mutations are single nucleotide missense mutations with damaging or unknown impacts on protein function. In the traditional model, PTEN regulates abnormal growth through suppression of PI3K/Akt/mTOR activity. However, the identification of new functions and links to non-canonical signalling cascades suggests a more complicated story. Previously, we have investigated the impact of these variants on PTEN signalling using flow cytometry. However, fluorescent spillover between channels greatly limits the number of markers that can be measured. Mass Cytometry, commonly known as CyTOF uses lanthanide conjugated antibodies that allow upwards of 40 markers to be measured simultaneously with greatly reduced signal overlap. Using CyTOF, we will be able to measure a greater number of markers throughout canonical and non-canonical PTEN signalling pathways. This will allow us to measure variant specific impacts on a wider range of PTEN functions. This methodology will lead to better characterization of the disease associated variants and the development of improved and personalized treatment options.

P3-G-758: MesoGAN: behavior generation from neural decoding of mesoscale cortical calcium dynamics using Generative Adversarial Networks.

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A fundamental goal of systems neuroscience is to understand the relationship between neural activity and behavior. Behavior has traditionally been characterized by low-dimensional, task-related variables such as movement speed or response times. More recently, there has been a growing interest in the automated analysis of high-dimensional video data collected during experiments. In this study, we introduce a Generative Adversarial Network (GAN) for synthesizing realistic behavioral videos from neural decoding of mesoscopic cortical calcium dynamics. The model is used to generate fake (predicted) behavioral videos from wide-field cortical calcium images. Our results demonstrate that the GAN-based approach can generate realistic fake behavioral videos that closely resemble the actual videos. The main contribution of this work is the development of a GAN-based framework for synthesizing realistic behavioral videos from neural signals. The framework can be used to generate a large number of fake behavioral videos, which can be used to test various hypotheses about the relationship between neural activity and behavior. Additionally, the attention maps generated by the GAN can identify key brain activity features that correspond to specific body movements. The results of this study provide new insights into the relationship between neural activity and behavior. By generating realistic fake behavioral videos from neural signals, we can better understand how changes in brain activity are related to changes in behavior. This knowledge can be used to develop new technologies for monitoring and controlling behavior, and it has important implications for fields such as brain-computer interfaces.

P3-G-759: Dendritic Polyglycerol Amine: An Enhanced Substrate to Support Long-Term Neural Cell Culture

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Long-term stable cell culture is a critical tool to better understand cell function. Most adherent cell culture models require a polymer substrate coating of poly-lysine or poly-ornithine for the cells to adhere and survive. However, polypeptide-based substrates are degraded by proteolysis and it remains a challenge to maintain healthy cell cultures for extended periods of time. Here, we report the development of an enhanced cell culture substrate based on a coating of dendritic polyglycerol amine (dPGA), a non-protein macromolecular biomimetic of poly-lysine, to promote the adhesion and survival of neurons in cell culture. We show that this new polymer coating provides enhanced survival, differentiation and long-term stability for cultures of primary neurons or neurons derived from human induced pluripotent stem cells (hiPSCs).

P3-G-760: Development of a mitochondrial specific T cell adoptive transfer mouse model of Parkinson?s disease.

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Growing evidence suggests that PINK1 and Parkin act as negative regulators of innate and adaptive immunity. The presentation of mitochondrial antigens (MitAP) can lead to the establishment of autoreactive mitochondrial specific T-cells in PINK1-KO mice after infections. However, the specific role of MitAP and mitochondrial specific T-cell in neuronal dysfunction in these mouse models of early-onset PD is presently unknown. To assess the role of MitAP and mitochondrial antigen-specific T-cells, we adoptively transferred activated mitochondria-specific CD8 T-cells or control CD8 T-cells recognizing ovalbumin into PINK1 KO or WT mice. The frequency and level of activation of these T-cells was assessed using flow-cytometry. The integrity of the dopamine system was assessed by immunohistochemistry and PD-like symptoms were assessed using the pole test and the open field. Activated mitochondrial antigen specific CD8 T cells developed into central memory T-cells after adoptive transfer. A subset of the mice died after a delay of 6-7weeks. Many of the surviving PINK1-KO and WT mice showed impaired performance in the pole test, open field and rotarod. The PD like pathology was found to be associated with infiltration of mitochondrial-specific CD8 T-cell in the brain. Preliminary data suggest that loss of DA neurons in the ventral midbrain and a reduction of their axon terminals in the striatum occurs in these mice. The present work supports the hypothesis that MitAP plays a role in the establishment of PD-like pathology in Pink1 mice via the response of mitochondria-specific T-cells. Moreover, the severity and progression of the disease seems to be linked to their infiltration to the CNS.

P3-G-761: Extracting structural connectomes from digital holographic microscopy phase images with deep-learning methods

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Digital holographic microscopy (DHM) has emerged as a powerful non-invasive imaging technique for studying living cells. DHM analysis focuses on a handful of cells for which identification can be done semi-automatically. Using this method does not scale up well and thus impedes analysis at the network level, which requires processing hundreds of cells from many samples. Therefore, we developed a new computational framework capable of performing fast, automatic, and accurate quantitative analysis, thereby allowing systematic analysis at the network level. Our framework takes a DHM phase image as input and returns a graph model, where nodes and edges respectively represent cell bodies and probable connections between them. The core of our framework relies on two U-Nets convolutional neural networks: one for cell-body and the other for neurite neuronal segmentation. It is completed by simple algorithms that combine the U-Nets results and detect the shortest path along the segmented neurites between each pair of cell bodies. We trained the U-Nets using manually segmented DHM phase images of rat neuron cultures. Moreover, we performed numerical experiments to assess the quality of the U-Nets prediction. The area under the mean receiver operating characteristic curves was 0.99 for cell-body and 0.97 for neurite segmentation, indicating almost perfect classification. We anticipate training our framework on human iPSC-derived neurons, allowing the comparison of networks between healthy cases and brain disease patients and could help discover new graph-based biomarkers.

P3-G-762: In vivo application of a genetically engineered optogenetic toolbox for neuronal cAMP & cGMP manipulation

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Cyclic AMP & GMP are major intracellular messengers, crucial for mediating sensory transduction and neuromodulation that serve for neurobiological processes such as synaptic plasticity. By utilizing genetically engineered light-sensitive cAMP/cGMP metabolic enzymes, which synthesize or hydrolyze cAMP/cGMP with light stimulation, we have previously shown the cAMP/cGMP-dependent spatiotemporal regulation of synaptic potentiation in acute murine hippocampal slices. Here, we introduce the application of our genetically-encoded optogenetic toolbox for cAMP/cGMP manipulation in living hippocampal neurons of freely-behaving mice to interrogate their spatiotemporal functions for learning and memory. By utilizing viral transduction methods with AAV, we successfully expressed the light-sensitive cAMP/cGMP metabolic enzymes to target hippocampal CA1 pyramidal neurons in the murine brain. Chronic brain implant of a wireless bilateral LED implant enables control of the timing and duration of optogenetic manipulation in freely-behaving animals. We demonstrate the application of this optogenetic technique for cAMP/cGMP manipulation in the intact CA1 hippocampus of freely-behaving mice during murine behaviour tests, such as the novel object recognition test, and demonstrate a rapid cAMP function in CA1 hippocampal neurons for object recognition memory. To further study how cAMP/cGMP regulate hippocampal neural circuit activities for learning and memory, we will discuss applications of our toolbox in combination with in vivo observation of neural activities by micro-endoscopy.

P3-G-763: A simple method for poly-D-lysine coating to enhance adhesion and maturation of primary cortical neuron cultures.

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Glass coverslips are used as a substrate since the first experiments with nerve cell cultures, conducted by Harrison in 1910. In 1974, the first study of brain cells seeded onto polylysine (PL) coated substrate was published. Usually, neurons adhere rapidly on PL coating. However, maintaining cortical neurons in culture on PL coating for a long period (i.e. more than 7 days) is a real challenge. We decided to find a simple method to enhance neuronal maturation on poly-D-lysine (PDL). Here, we present a collaborative study, conducted between chemical engineers and neurobiologists. In this work, we detailed and characterized a simple protocol to coat PDL efficiently on coverslips, and we compared it to the conventional adsorption method. We next studied adhesion and maturation of primary cortical neurons with many complementary anatomical and functional approaches including phase contrast microscopy, immunocytochemistry, scanning electron microscopy, patch clamp recordings and calcium imaging. We observed that several parameters of neuronal maturation were influenced by the substrate. Indeed, neurons developed more dense and extended networks, and synaptic activity was enhanced, when seeded on covalently bound PDL compared to adsorbed PDL. Hence, we established reproducible and

optimal conditions enhancing a healthy maturation of primary cortical neurons in vitro. Neuronal cultures are often used as a first screening approach. Our method will allow higher reliability and yield of results and could also be profitable for laboratories using PL with other cell types.

P3-G-764: Automatic synthesis of astrocytic trees in silico through generative modeling

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Astrocytes are prominent glial cells in the brain that shape the anatomy and function of our neural circuits. They do so thanks to their complex branched morphology, which infiltrates the neural tissue and wraps around key neuronal elements, allowing modulation of neural activity by various biochemical pathways through the sites of contact. Characterizing astrocytes branched anatomy is key to understanding their functions in brain circuits. However, there is currently no systematic framework for such a characterization. We present a preliminary automated pipeline to systematically classify astrocyte anatomy based on the extraction of macro- and micro-features from experimental 3D astrocyte tracing. Macro-features are scalar measurements that quantify cell anatomy globally. Micro-features are instead vectorized by the multiple branching compartments of the cell. Deploying techniques from statistics, machine learning, and topological analysis we mine for patterns of macro- and micro-features that completely describe the astrocyte branching architecture. In turn, we use a generative modeling approach to simulate those patterns de novo and synthesize realistic astrocyte membrane scaffolds.

P3-H-765: Accounting for multiscale processing in real-world decision-making: Hippocampal contributions in bridging model-free and model-based strategies

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For adaptive decision making in real-world contexts, the brain needs to allow past information to influence current processing over multiple timescales, enabling a complex and reciprocal dynamics between the two underlying reinforcement learning strategies: model-free (MF)--a reflection of the past--and model-based (MB)--a deliberation on causal environment-behavior structure. Yet, while the role of the hippocampus in memory and spatial learning is well-known, its interactions with the striatum with regards to decision-making is just starting to be explored. This paper motivates the necessity to better appreciate the role of the hippocampus in decision-making. We review literature in reinforcement learning that examines the successor representation (i.e., an expectation of future states from a given starting state) as a means to bridge MF and MB strategies. Alongside, we review hippocampal sequences and show that the implementation of such sequences in reinforcement learning agents improves their performance. This also enables the agents to perform multiscale temporal processing. Altogether, the paper will articulate a framework to advance current striatal-focused decision making to better account for multiscale mechanisms underlying various time-related concepts such as the self that cumulates over a person's life course.

Abstracts
16th Canadian Neuroscience Meeting
May 28- 31, 2023, Montreal, Canada

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