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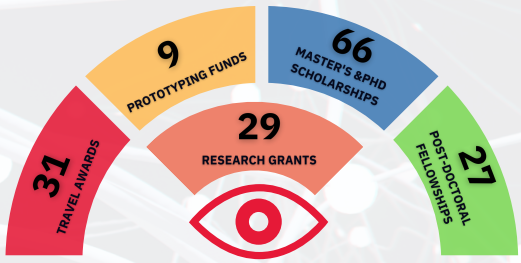

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Parallel symposium 1: Neurovascular function in health and disease

Presenters: Baptiste Lacoste, University of Ottawa; Caroline Ménard, Université Laval (Chair); Mike Sapieha, Université de Montréal; Craig Brown, University of Victoria

Cerebrovascular health is critical for a properly functioning nervous system. All aspects of the neurovasculature are tightly regulated in the healthy brain, including developmental processes such as angiogenesis and pruning, structures like the blood-brain barrier (BBB), and coupling between blood flow and neural activity. In advanced age and diseases, mechanisms governing cerebrovascular structure and function can go awry, which has profound implications on sensory, motor and cognitive abilities. This symposium brings together a diverse group of early/mid-career Canadian scientists exploring these issues. First, Dr. Lacoste will reveal how neurovascular dysfunction is involved in neurodevelopment disorders such as autism. Second, Dr. Menard will discuss the effects of stress resilience vs depression on BBB integrity and function. Next, Dr. Sapieha will describe how the innate immune system senses/remodels pathological blood vessels in the CNS with a focus on the retina. Finally, Dr. Brown will describe the factors influencing brain region-specific vessel loss that naturally occurs during aging.

Cerebrovascular deficits in autism

Baptiste Lacoste[1]

[1]*Ottawa Hospital Research Institute, University of Ottawa*

BACKGROUND AND AIM: Brain development relies on proper maturation of its vascular beds that not only ensure steady supply of oxygen and nutrients, but also support the proliferation and differentiation of neural progenitors. As such, alterations in cerebrovascular processes during development may have long-lasting neurodevelopmental consequences, but direct evidence supporting this concept is missing. Autism spectrum disorders (ASD) are neurodevelopmental conditions that affect attention, memory, learning, motor coordination, language, speech and social interactions. While the neuronal underpinnings of ASD are being extensively studied, whether vascular deficits play a role in ASD onset and/or progression is still unknown. The aim of our study is to address this important knowledge gap. METHODS: We investigated the maturation of cerebrovascular networks in 16p11.2df/+ mice, a robust mouse model of the 16p11.2 deletion ASD syndrome. In addition, we achieved endothelial-specific deletion of the 16p11.2 locus by CRE-mediated recombination under the control of an endothelial promoter (Cdh5-Cretg/+;16p11.2flox/+). Using both constitutive and conditional mutants and their Wild-Type littermates, we quantified neurovascular structure and function in vivo and in vitro, and assessed mouse behavior. RESULTS: We demonstrate that 16p11.2 hemizygosity leads to endothelium-dependent structural and functional neurovascular abnormalities. In 16p11.2df/+ mice, endothelial dysfunction manifested by impaired cerebral angiogenesis at postnatal day (P) 14, and by altered neurovascular coupling and cerebrovascular reactivity at P50. Defective angiogenesis was confirmed in vitro using primary 16p11.2df/+ mouse brain endothelial cells. Finally, we found that mice with endothelium-specific 16p11.2 deletion partially recapitulated ASD behavioral traits, including locomotor hyperactivity and impaired motor learning. CONCLUSIONS: By showing that endothelial

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16p11.2 homozygosity is required for normal brain maturation, our findings identify endothelial cells as substantial contributors to ASD, opening new research avenues.

Molecular adaptations of the blood-brain barrier promote stress resilience vs depression

Katarzyna Dudek[1], Laurence Dion-Albert[1], Manon Lebel[1], Katherine LeClair[2], Simon Labrecque[3], Ellen Tuck[4], Carmen Ferrer Perez[5], Sam Golden[6], Carol Tamminga[7], Gustavo Turecki[8], Naguib Mechawar[8], Scott Russo[2], Caroline Ménard[1]

[1]Université Laval, [2]Icahn School of Medicine at Mount Sinai, [3]CERVO Brain Research Center, [4]Trinity College Dublin, [5]University of Valencia, [6]University of Washington, [7]University of Texas Southwestern, [8]McGill University

BACKGROUND: 30-50% of depressed individuals are unresponsive to commonly prescribed antidepressant treatments, suggesting that biological mechanisms, such as stress-induced inflammation and blood vessel dysfunction which are receiving increased attention in psychiatry, remain untreated. The blood-brain barrier (BBB) is the ultimate frontier between the brain and harmful toxins or inflammatory signals circulating in the blood. Preclinical and clinical studies suggest that inflammation and vascular dysfunction contribute to the pathogenesis of major depressive disorder. Chronic social stress alters BBB integrity through loss of tight junction protein claudin-5 (cldn5) in mice, promoting passage of circulating proinflammatory cytokines and depression-like behaviors. This effect is prominent within the nucleus accumbens (NAc) in males, a brain region associated with mood regulation; however, the mechanisms involved are unclear. Moreover, compensatory responses leading to proper behavioral strategies and active resilience are poorly known. METHODS: We combined behavioral, pharmacological, and cell-specific gene profiling experiments in mice with epigenetic, molecular, and anatomical analysis of human samples to unravel mechanisms with therapeutic potential to protect the brain and promote resilience. RESULTS: We identified active molecular changes within the BBB associated with stress resilience that might serve a protective role for the neurovasculature. We also confirmed the relevance of such changes to human depression and antidepressant treatment. We showed that permissive epigenetic regulation of cldn5 expression and low endothelium expression of repressive cldn5-related transcription factors are associated with stress resilience. Region- and endothelial cell-specific whole transcriptomic analyses revealed molecular signatures associated with stress vulnerability vs resilience. We identified proinflammatory TNFα/NFκB signaling and hdac1, an epigenetic-related enzyme, as mediators of stress susceptibility. Pharmacological inhibition of stress-induced increased in hdac1 activity rescued cldn5 expression in the NAc and promoted resilience. Importantly, we confirmed changes in HDAC1 expression in the NAc of depressed patients without antidepressant treatment in line with CLDN5 loss. Conversely, many of these deleterious CLDN5-related molecular changes were reduced in postmortem NAc from antidepressant-treated subjects. CONCLUSIONS: These findings reinforce the importance of considering stress-induced neurovascular pathology in depression and provide therapeutic targets to treat this mood disorder and promote stress resilience.

Cellular Senescence and Retinal Vascular Disease

Przemyslaw (Mike) Sapieha[1], Mike (Przemyslaw) Sapieha[1]

[1]University of Montreal

Pathological retinal neovascularization is the hallmark of primary blinding diseases across all age groups, yet surprisingly little is known about the causative factors. These diseases include diabetic

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retinopathy and retinopathy of prematurity where progressive decay of retinal vasculature yields zones of neural ischemia. These avascular zones and the hypoxic neurons and glia that reside in them are the source of pro-angiogenic factors that mediate destructive pre-retinal angiogenesis. This lecture will focus on how cellular senescence, a dynamic and typically terminal cellular response to various stressors often associated with aging, influences progression of retinopathies. Specifically, the contribution of cellular senescence to pathological angiogenesis and vascular remodeling will be discussed.

Microvascular remodeling is governed in a brain region specific and age dependent manner

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

[1]University of Victoria

It should be no surprise that the microvasculature, which helps meet the ever changing metabolic demands of the brain and all its components, is highly heterogeneous in its architecture/function and changes throughout the lifetime of the animal. However, there are significant gaps in our knowledge concerning whether: a) there are region specific differences in microvascular density, length and tortuosity, b) whether there are brain-region specific vulnerabilities to vessel loss with aging, and what factors could predict such losses, and c) whether structural remodelling in the form of angiogenesis and vessel pruning varies across brain regions and what molecular mechanisms control this plasticity. In order to address these questions, we imaged fluorescently labelled vasculature in 15 different brain regions and quantified vessel length, tortuosity and diameter in young adult and aged mice. Our data show that vessel loss was most pronounced in white matter (corpus callosum) followed by cortical, then subcortical grey matter regions, while some regions (visual cortex, amygdala, thalamus) showed no decline with aging. Vessel width and tortuosity generally increased with age but neither reliably predicted regional vessel loss. Since capillaries are naturally prone to plugging and prolonged obstructions often lead to vessel pruning, we hypothesized that regional susceptibilities to plugging could help predict vessel loss. By mapping the distribution of microsphere-induced capillary obstructions, we discovered that regions with a higher density of persistent obstructions were more likely to show vessel loss with aging and vice versa. Since capillary plugging could not fully account for region specific differences in vessel loss with age, we imaged blood vessels over several weeks in regions that did or did not show vessel loss (eg. retrosplenial vs visual cortex, respectively). Of note, retrosplenial cortex reliably exhibited vessel pruning but incidences of angiogenesis were exceedingly rare. By contrast, microvascular networks in visual cortex, were brimming with examples of sprouting capillaries, primarily within the first 250µm of cortical depth. Imaging these same regions in mice with conditional, endothelial specific knockdown of VEGF-R2 revealed significantly fewer angiogenic and pruning events. Our findings reveal a striking, and underappreciated brain region specific diversity in microvascular plasticity and susceptibility to the effects of aging. This work was funded by CIHR, NSERC, HSFC and MSFHR.

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Parallel symposium 2: The hypothalamus and its hormones in health & disease

Presenters: Melissa Chee, Carleton University; Masha Prager-Khoutorsky, McGill University (Chair); Katrina Y Choe, McMaster's University; Tamás Füzesi, University of Calgary

The hypothalamus accounts for less than 1% of brain tissue yet it controls most primitive and vital functions of the organism, including hunger, thirst, and reproduction. Hypothalamic neuroendocrine systems regulate a variety of physiological processes including energy metabolism, fluid homeostasis, lactation and parturition, and behavioral responses to stress. Moreover, recent findings implicate centrally released neurohormones in the pathophysiology of cognitive and psychiatric disorders (e.g. autism), as well as metabolic and cardiovascular diseases (e.g. diabetes and hypertension). The proposed symposium will feature timely topics and highlight recent advances in our understanding of how the hypothalamus contributes to health and disease. A line-up of early-career investigators will focus on subjects ranging from basic mechanisms of humoral control of metabolic and hemodynamic homeostasis, to complex emotional states. The speakers will also discuss the role of neuroendocrine system regulation in obesity, salt-sensitive hypertension, and autistic spectrum disorders.

Melanin-concentrating hormone receptors in the regulation of metabolic health

Melissa Chee[1], Carl Spencer[1], Alex Hebert[1], Nadege Briancon[2], Pavlos Pissios[2], Eleftheria Maratos-Flier[2]

[1]Carleton University, [2]Beth Israel Deaconess Medical Center

BACKGROUND AND AIM: Melanin-concentrating hormone (MCH) is a key player in the maintenance of metabolic health and is produced exclusively within the lateral hypothalamus. Activation of MCH neurons is implicated in obesity, and the deletion of MCH or MCH neurons leads to hyperactivity, including baseline and dopamine-mediated hyperactivity, and weight loss. However, the neural targets and transmitter systems that support the obesogenic effects of MCH are lesser known because MCH receptors (MCHR1) are widespread throughout the brain. We found prominent expression of Mchr1 mRNA in the striatum that includes the accumbens nucleus, which is comprised almost entirely of GABAergic medium spiny neurons and mediate the hyperlocomotor effects of dopamine. We thus determined if MCH acts at GABAergic neurons to regulate energy homeostasis by deleting Mchr1 from GABAergic neurons expressing the vesicular GABA transporter Vgat. METHODS AND RESULTS: We generated a Mchr1-flox mouse and crossed it to the Vgat-cre mouse to delete Mchr1 specifically from GABAergic neurons throughout the brain. The resulting Vgat-Mchr1-KO mice have lower body weights and robust hyperactivity. In order to identify candidate GABAergic neurons underlying this hyperactivity, we delivered an adeno-associated virus encoding cre recombinase to the accumbens nucleus of Mchr1-flox mice and showed that Mchr1 deletion restricted to the accumbens also recapitulated the hyperactivity of Vgat-Mchr1-KO mice. As loss of MCH increase striatal dopamine tone, we determined if a heightened dopamine tone underlie the hyperactivity of Vgat-Mchr1-KO mice. Systemic treatment of Vgat-Mchr1-KO mice enhanced the hyperlocomotor effects of the dopamine reuptake blocker GBR12909. We used amperometry recordings to directly assess dopamine tone in the accumbens and found that GBR12909 also produced a greater increase in dopamine current within brain slices from Vgat-Mchr1-KO mice.

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Interestingly, we found that while MCH acutely suppressed dopamine release in wildtype accumbens, this inhibitory MCH effect was abolished in brain slices from Vgat-Mchr1-KO mice. CONCLUSION: In aggregate, these findings show that MCH regulates dopamine release, and the interaction between the dopaminergic and GABAergic systems in the accumbens comprise a critical pathway underlying the effects of MCH in metabolism and the expression of metabolic health.

Vasopressin neurons and their role in salt-dependent hypertension

Masha Prager-Khoutorsky[1]

[1]McGill University

BACKGROUND AND AIM Vasopressin neurons are an integral part of the magnocellular neuroendocrine system, playing a key role in water and salt homeostasis. Increases in plasma sodium and osmolality activate magnocellular vasopressin neurons, resulting in enhanced vasopressin release from their nerve terminals located in the posterior pituitary into the peripheral circulation. Magnocellular vasopressin neurons are intrinsically osmosensitive and are activated by cell shrinking in response to increased extracellular sodium levels and osmolality. Our recent studies demonstrated that magnocellular vasopressin neurons harbor a unique cytoskeletal scaffold attached to ion channels on the cell surface, which translates cell shrinking into mechanical activation of the channels, leading to the increase in the firing rate of the neurons and enhanced vasopressin release. In addition to the intrinsic mechanisms mediating the activation of magnocellular neurons, extrinsic factors contribute to the stimulation of magnocellular neurons and vasopressin release via synaptically-mediated inputs arising from sodium and osmolality sensing neurons located in several interconnected hypothalamic nuclei. Additionally, local glial cells play an important role in controlling the activity of magnocellular neurosecretory cells. Our goal is to understand molecular and cellular mechanisms controlling the activity of vasopressin neurons in healthy organisms and pathological conditions. METHODS We use a combination of cellular, molecular, and whole organism analysis to study the role of vasopressin neurons in healthy animals and in rat models of salt-dependent hypertension. The methodologies include superresolution imaging, electrophysiology, and hemodynamic measurements in freely moving animals. RESULTS Our data indicate that a chronic exposure of rats to high dietary salt by replacing their drinking water with 2% NaCl for 7 days (salt loading), leads to an increase in the density of cytoskeletal networks in magnocellular vasopressin neurons. We hypothesize that increases in the cytoskeletal density contribute to hyperactivation of vasopressin neurons in this condition. Our data suggest that mDia1, a downstream effector of RhoA, is involved in the regulation of cytoskeleton in vasopressin neurons. We propose that mDia1 mediates the increase in the cytoskeleton density in vasopressin neurons following salt loading, thereby contributing to hyperactivation of magnocellular vasopressin neurons. In addition, our data suggest that microglia activation and astrocyte remodeling in the magnocellular system can also contribute to the increased activation of vasopressin neurons following salt loading. CONCLUSIONS Our results suggest that both intrinsic and extrinsic mechanisms regulating the activity of vasopressin neurons in healthy organisms and their malfunction can lead to increased neuronal activation, contributing to pathological conditions such as salt-dependent hypertension.

The role of central oxytocin system in autism-related social impairment

Katrina Choe[2], Richard Bethlehem[2], Martin Safrin[2], Hongmei Dong[2], Ying Li[2], Elena Salman[2], Qiuli Bi[2], Valery Grinevich[3], Peyman Golshani[2], Laura DeNardo[2], Olga Penagarikano[4], Neil Harris[2], Daniel Geschwind[2]

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[1]McMaster University, [2]University of California, Los Angeles, [3]Zentralinstitut für Seelische Gesundheit (ZI), University of Heidelberg, [4]University of the Basque Country

Aberrant functional connectivity is frequently found in autism spectrum disorders (ASD), notably correlating with the degree of social impairment (Supekar et al., 2013). We previously reported that administration of oxytocin improves social deficits in mice lacking an ASD risk gene, Cntnap2 (Penagarikano et al., 2015). Given the ability of oxytocin to increase circuit signal-to-noise (Owen et al., 2013), we hypothesized that oxytocin might exert its pro-social effects via stimulating socially-relevant brain regions and rescuing potentially present FC alterations in Cntnap2 KO mice. To test this, we used high field (7T) functional magnetic resonance imaging (fMRI) to measure brain-wide BOLD responses and changes to resting-state functional connectivity after administering oxytocin to wild-type and Cntnap2 KO mice. We found that a set of brain regions with established roles in social behavior (e.g. paraventricular nucleus of the hypothalamus (PVN), nucleus accumbens (NAc), medial prefrontal cortex) are more weakly connected together in KO mice compared to wild-type controls. In contrast, these regions were more strongly connected to the rest of the brain in KO mice. Strikingly, oxytocin robustly increased the BOLD signal in these social regions, and reversed both functional connectivity phenotypes in these mice, results we validated with brain-wide c-Fos activity mapping using iDISCO combined with lightsheet imaging. Stimulating endogenous release of oxytocin from the PVN using excitatory DREADD led to identification of NAc as a potential key region for contributing to oxytocin's pro-social effects in Cntnap2 KO mice. To directly test this hypothesis, we examined the effects of either infusing TGOT (oxytocin receptor agonist) into the NAc, or optogenetically stimulating the local release of oxytocin onto the NAc on social behavior of KO mice. Indeed, we found that both treatments significantly increased social interaction with a novel mouse, confirming our hypothesis. Collectively, these results suggest that the pro-social effects of oxytocin in Cntnap2 KO mice may involve promotion of concerted activity across social brain regions, and identify the NAc as a key region in this process.

Representation of emotion state in the hypothalamus

Tamás Füzesi[1], David Rosenegger[1], Neilen Rasiah[1], Nuria Daviu[1], Leonardo Molina[1], Taylor Chomiak[1], Wilten Nicola[1], Jaideep Bains[1]

[1]Hotchkiss Brain Institute

BACKGROUND AND AIM: Emotions affect cognition, influence behaviour and drive somatic responses. Discrete events can trigger persistent emotional states that show contextual recall. Under these conditions, the detection of an emotion state is inferential, relying on an accurate readout of a motor action. In rodent models, contextual recall of an aversive experience induces freezing behavior which habituates with repeated exposure. Does this mean the emotional state associated with this experience has also been resolved? Unlike behavior, hormonal changes associated with negative emotional states are less likely to habituate to repeated exposure. This suggests that the brain relies on distinct memory mechanisms to link emotional experiences to behavior and somatic responses. METHODS: We utilized in vivo single fiber photometry and miniature microscopy using GCaMP6 expression in CRH-Cre transgenic mice in combination with computational approaches. RESULTS: The hypothalamus coordinates somatic adjustments to emotion states triggered by discrete events. Here we show that exposure to an aversive context triggers an "upstate" in the activity of corticotropin releasing hormone neurons in the hypothalamic paraventricular nucleus (CRHPVN). Utilizing in vivo imaging of neuronal activity and computational approaches we demonstrate that upstates have larger dimensional dynamics, reflecting an increase in desynchronized activity of individual cells due to local processing through a distributed network. This

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upstate is reliably recalled in a contextually-sensitive fashion even after behavioral responses have been extinguished. Furthermore, the relative amplitude of the upstate is a reliable indicator of different degrees of emotional valence. CONCLUSIONS: Our findings show that CRHPVN neurons encode scalable central emotion states that reflect the valence of prior experience but are uncoupled from outward behavioural readouts.

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Parallel symposium 3: Emerging role of microglia in neurodegeneration

Presenters: Tiina Kauppinen, University of Manitoba (Chair); Jasna Kriz, Université Laval; Jason Plemel, University of Alberta; Deborah Kurrasch, University of Calgary

The immune system is tightly associated with all injury and diseases of the central nervous system. Microglia, the resident immune cells of central nervous system initiate immune responses and drive overall neuroinflammation. Apart from immune responses, microglia have also role in synaptic plasticity. Microglial synaptic pruning and trophic factor release allow them to eliminate, prune and remodel synapses. Injury, disorder, inflammation or mere aging can jeopardize the control of these microglial functions resulting chronic neuroinflammation, altered synaptic connections, synaptic loss and dysfunction. Indeed, increasing evidence suggest a key role for microglia in neurodegenerative and neurodevelopmental conditions. Gaining a greater understanding of physiological functions and regulation of these cells is critical as it can reveal how microglial varying functions impact brain development, health and progression of neurodegenerative disorders. In this symposium we will present latest data revealing microglial roles in different disease contexts (Alzheimer's disease, ischemic stroke, white matter injury and neurodevelopmental disorders) and address sexual dimorphism.

Microglial cells drive the development of cognitive impairment

Tiina Kauppinen[1]

[1]University of Manitoba

BACKGROUND AND AIM: Microglia, the resident immune cells of central nervous system initiate immune responses and drive overall neuroinflammation. Apart from immune responses, microglia have also role in synaptic plasticity. Microglial synaptic pruning and trophic factor release allow them to eliminate, prune and remodel synapses. Injury, disorder, inflammation or mere aging can jeopardize the control of these microglial functions resulting chronic neuroinflammation, synaptic loss and dysfunction. Indeed, increasing evidence, though indirect, suggest a key role for microglia in neurodegenerative disorders resulting cognitive deficits. Our previous in vitro studies have demonstrated that the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP-1) regulates microglial functions. Here, we used novel molecular tools allowing microglia-specific modulations of PARP-1 in in vivo to directly test the hypothesis that microglial inflammatory and synaptotoxic functions contribute to progression of cognitive deficits. METHODS: Microglial modulations included two microglia-targeting contrary approaches; conditional PARP-1 knockout (PARP-1cKO) mice and lentiviral transduction of continuously active PARP-1 (LV-Iba1-PARP-1on). The effects of microglial PARP-1 deletion was assessed in triple-transgenic AD (3xTg-AD) mice crossed with CD11b-cre-driven PARP-1cKO mice. The disease progression was evaluated in 5-month-old mice by analyzing AD associated cognitive deficits in novel object recognition (NOR) test and synaptic decline via immunohistochemistry (IHC; synaptophysin) analysis and electrophysiology recordings. Neuroinflammation was assessed by IHC analysis (Iba-1, GFAP) of glial cells and by cytokine profiling. Prolonged microglial PARP activation was induced in healthy 7 weeks old mice by stereotaxic hippocampal injection of LV-Iba1-PARP-1on and outcomes were evaluated at 14 weeks of age as above with AD mice. RESULTS: Microglial PARP-1 deletion reduced neuroinflammation in 3xTg-AD

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mice as seen by decreases in microglial number and morphological activation, astrogliosis, and pro-inflammatory cytokine levels. Microglial PARP-1 deletion prevented impaired NOR test performance and synaptic decline in AD mice, suggesting that PARP-1-dependent microglial functions contribute to the synaptic decline and cognitive deficits associated with AD. This point was highlighted by CA1 hippocampal field recordings showing that the reduction in long-term potentiation (LTP) seen upon Aβ infusion in WT mice was prevented in PARP-1cKO brain sections. Further, induction of prolonged microglia PARP-1 activation in healthy mice induced neuroinflammation, synaptic decline and cognitive deficits. CONCLUSIONS: Our study provides direct evidence of microglial importance in development of cognitive deficits. PARP-1 targeting allows preventing microglial functions that promote neuroinflammation and synaptic decline, suggesting therapeutic relevance for various neurodegenerative disorders.

Microglial cells after brain injuries:sexually dimorphic and lost in translation

Jasna Kriz[1]

[1]*Laval University*

BACKGROUND AND AIM: Microglia are the principal immune cells of the brain. The consensus today is that once activated microglia/macrophages can acquire a wide repertoire of profiles ranging from the classical pro-inflammatory to alternative and more protective phenotypes. Over the past decade, we and others have shown that optimal and timely activation of microglial cells and innate immunity is instrumental in the control of the inflammation-induced damage to CNS. To add to complexity, increasing evidence suggests a marked sexual dimorphism in the processes associated with microglial activation following different types of brain injuries. At present, the in vivo molecular mechanisms involved in the control of microglia and/or macrophage immune profiles remain elusive METHODS: To decipher the molecular mechanisms underlying microglial activation in vivo, we created a transgenic model in which Flag/EGFP was fused to the N-terminus of the large subunit ribosomal protein L10a and expressed under the transcriptional control of a myeloid specific gene promoter Thus, a simple high affinity immunoprecipitation assay from brain homogenates allows a pull down of the transcriptome and/or proteome from the targeted cell type. By isolating both ribosome-attached mRNAs and peptides, we obtained a snapshot of the dynamic translational state of microglial ribosomes with mRNAs as input and newly synthesized peptides as output. Using this strategy, we identified mRNA and protein signatures associated with microglial activation. RESULTS: By using in vivo model-system for analysis of dynamic translational state of microglia ribosomes with mRNAs as input and newly synthesized peptides as an output, we discovered a marked dissociation of microglia mRNA and protein networks following innate immune challenge. We found that the highly up-regulated and polysome- associated mRNAs are not translated resulting in two distinct and rather divergent microglia molecular signatures: i) a highly specialized immune and pro-inflammatory mRNA signature and ii) a more immunomodulatory and homeostatic protein signature. As molecular mechanism, we discovered a selective 3'UTR-mediated translational suppression of highly expressed immune mRNAs. Furthermore, we identified a novel and previously unknown role for RNA binding protein Serine/Arginine-Rich Splicing Factor 3 SRSF3 as a master suppressor/regulator of innate immune genes translation in activated microglia. CONCLUSIONS: Our recent work suggests involvement of SRSF3 -mediated mechanisms in the modulation of immune profiles of activated microglia in different type of brain injuries and/or pathologies. Better understanding of SRFS3- mediated immunomodulation may open new avenues for therapeutic modulation of innate immune response following brain injuries.

Microglia response to demyelination: a mixed bag

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Jason Plemel[1]

[1]*University of Alberta*

Background and Aim: Microglia and infiltrating macrophages are thought to orchestrate the central nervous system (CNS) response to injury; however, similarities between these cells make it challenging to distinguish their relative contributions. Methods: We genetically labelled microglia and CNS-associated macrophages to distinguish them from infiltrating macrophages. We also used single-cell RNA sequencing of genetically labelled microglia to understand their response to demyelination Results: We describe multiple microglia activation states that change over time, one of which was enriched for interferon associated signalling. Although blood-derived macrophages acutely infiltrated the demyelinated lesion, microglia progressively monopolize the lesion environment where they surrounded infiltrating macrophages. In the microglia-devoid sciatic nerve, the infiltrating macrophage response was sustained. In the CNS, the preferential proliferation of microglia and sparse microglia death contributed to microglia dominating the lesion. Microglia ablation reversed the spatial restriction of macrophages with the demyelinated spinal cord, highlighting an unrealized macrophages-microglia interaction. Conclusions: We identify distinct responses to demyelination between microglia and CNS-infiltrating macrophages. The restriction of peripheral inflammation by microglia may be a previously unidentified mechanism by which the CNS maintains its "immune privileged" status.

Embryonic hypothalamic microglia: a sensor for maternal stressors and potential mediator of neurodevelopmental diseases

Jessica Rosin[1]*, Faizan Malik*[1]*, Deborah Kurrasch*[1]

[1]*University of Calgary*

Microglia are the resident immune cells in the central nervous system (CNS). Originally thought to be primarily responsible for disposing of cellular debris and responding to neural insults, emerging research now shows that microglia are highly dynamic cells involved in a variety of neural processes, including development. The hypothalamus is a brain region critical for maintaining homeostatic processes such as energy balance, thirst, food intake, reproduction, and circadian rhythms. Given that microglia colonize the embryonic brain alongside key steps of hypothalamic development and that the loss of microglia causes obesity in newborn pups, consistent with a defect in neuroendocrine signaling, we explored how microglia influence these nearby hypothalamic progenitors. We found that embryonic microglia directly and indirectly interact with hypothalamic radial glial cells by both touching and clipping of their projections and also by releasing signaling cues, respectively. These interactions were increased following maternal stress, suggesting that fetal microglia might be sensors to the external environment. Combined, these data demonstrate that microglia can influence overall development of this important brain region, which might contribute to diseases later in life.

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Parallel symposium 4: Intersections between chloride homeostasis and synaptic communication in health and disease

Presenters: Isabel Plasencia-Fernandez, Université Laval; Jaideep Bains, University of Calgary; Rochelle Hines, University of Nevada at Las Vegas; Nicholas Weilinger, University of British Columbia (Chair)

Chloride homeostasis is fundamental to brain health. As an electrolyte, chloride gradients establish GABAergic inhibition to tune excitatory/inhibitory balance and shape synaptic coding. As an osmolyte, chloride is a key determinant of neuronal volume. Intracellular chloride is therefore tightly controlled in neurons by chloride cotransporters, particularly KCC2, to preserve healthy synaptic communication. This symposium will cover new insights into how neuronal chloride is regulated, with emphasis on chloride dysregulation in synaptic pathology. Isabel Plasencia will discuss how different signaling pathways interact to modulate chloride gradients through KCC2 activity. Jaideep Bains will talk on the synaptic implications of stress-induced chloride dysregulation in the hypothalamus. Rochelle Hines will address how a loss of GABAergic contacts on the axon initial segment results in developmental seizures despite a protracted switch to hyperpolarizing GABA currents in this compartment. Finally, Nicholas Weilinger will demonstrate a novel imaging technique to uncover chloride microdomains that drive dendritic swelling in stroke.

Differential regulation of KCC2 function, internalization and degradation via TrkB and NMDA receptor signaling

Isabel Plasencia Fernandez[2], Marc Bergeron[2], Antoine Godin[1], Yves de Koninck[1]

[1]Université Laval, CERVO Research Centre, [2]Laval University/CERVO Brain Research Centre

BACKGROUND: Chloride homeostasis is tightly regulated in neurons as it defines the inhibitory synaptic strength and shapes plasticity. The K+-Cl- cotransporter KCC2 is a key molecule to determine the intracellular Cl- in neurons thus, to define Cl- homeostasis. KCC2 hypofunction appears at the root of several neurological disorders, emphasizing the importance of studying its regulatory mechanisms. Both BDNF-TrkB and NMDA receptor (NMDAR) signaling regulate KCC2, but their specific contribution to this regulation and how they interact remains unknown. METHODS: to quantify KCC2 protein levels we used a biotinylation protocol that allows to differentiate between the plasmalemmal and total protein through western blot. Functional assessments in neurons were performed by electrophysiological patch-clamp recordings of the GABA reversal potential by imposing a chloride load into the cell and by fluorescence lifetime imaging of the chloride indicator MQAE. Functional KCC2 validations in oocytes were performed by Rb+-influx assays in Xenopus laevis oocytes. RESULTS: We found that TrkB and NMDAR signaling pathways act synergistically to differentially modulate KCC2 function and expression, via distinct Ca2+ signalling modes. TrkB-signalling in absence of NMDAR activation modulates KCC2 function through intracellular Ca2+ release but does not affect expression. In contrast, NMDAR activation regulates first KCC2 internalization, and then degradation, in an extracellular Ca2+ influx and time-dependent manner. Additionally, we found that the KCC2 modulation mediated by NMDAR signaling is potentiated by TrkB pathway stimulation and that prolonged inhibition of KCC2 activity caused NMDAR-dependent KCC2 downregulation. CONCLUSIONS: Together, these findings reveal that KCC2 function can be regulated through other means than membrane expression. Differential regulation of KCC2 function

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and expression occurs across a spectrum of time scales and through distinct, yet convergent pathways.

Using optical tools to probe chloride (dys)regulation in stress circuits

Jaideep Bains[1], Aaron Lanz[1]

[1]University of Calgary

In mammals, an immediate threat activates multiple, interconnected neural networks to launch an innate behavioral program that maximizes the probability of survival. These networks also drive corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) to release hormones that allow the animal to cope in the face of challenge and restore homeostasis. CRH neurons are tightly regulated by inhibitory GABA synapses. The initiation of the endocrine cascade requires a dephosphorylation of the K-Cl co-transporter, KCC2, which compromises Cl buffering and depolarizes the ECl. Although the downregulation of KCC2 has been linked to alterations in cell output, the intricacies of chloride dysregulation on circuit function have not been fully explored. Fluctuations in chloride could alter spike pattern generation to promote bursting or alter population encoding. Additionally, GABA-mediated calcium spikes could change plasticity rules at inhibitory and excitatory synapses. To study chloride homeostasis in hypothalamic CRH neurons, we exploited the light-sensitive inward chloride pump, halorhodopsin, to manipulate chloride gradients with high temporal precision. We show that in cells expressing this pump, photostimulation is sufficient to collapse the Cl gradient at GABA synapses; the recovery from this collapse is rapid (approximately 5 s). Pharmacological inhibition of KCC2 or acute stress prolonged the recovery following Cl loading and also revealed an increase in bursting activity in CRH neurons. Furthermore, inhibition of KCC2 was also sufficient to gate an activity-dependent form of metaplasticity at glutamate synapses onto CRH neurons. We propose that local chloride gradients in CRH neurons control membrane excitability to regulate dendritic peptide release and plasticity at neighbouring synapses.

Modeling developmental epilepsy by manipulating GABA signaling at the axon initial segment

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Seizures are one of the most common neurological conditions identified in humans, with highest incidence during the first year of life. The hyperexcitability observed early in brain development arises in part from a lack of chloride extrusion in neurons, rendering GABAergic signaling depolarizing instead of hyperpolarizing. In balance with this, many types of seizures are thought to arise from a failure of inhibitory GABAergic signaling known to be essential for patterning neural activity. GABAergic synapse subtypes that fall on the axon initial segment (AIS) are attractive candidates for control of activity patterns due to proximity to the site of action potential generation. The AIS shows a late developmental shift around postnatal day 30 to hyperpolarizing GABA, suggesting that early GABAergic signaling on the AIS is depolarizing. We have recently developed a mouse model of developmental epilepsy bearing a mutation in the GABAA receptor α2 subunit large intracellular loop (Gabra2-1). This mutation interferes with α2 clustering at the AIS, and causes a loss of AIS synapses. Despite this loss of depolarization at the AIS, Gabra2-1 mice show spontaneous seizures and mortality beginning as early as day 9 of postnatal development, with peak mortality on day 20. Mortality is rarely seen past 25 days, suggesting a window of time where signaling via GABAA receptors containing the α2 subunit may be key for hyperexcitability and seizure susceptibility. We

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have found that the Gabra2-1 mutation influences the structure and organization of AIS constituents including voltage gated channels and associated anchoring proteins early in development, prior to the formation of inhibitory synapses onto the AIS. Our findings suggest that GABAergic signaling via GABAA receptors containing the α2 subunit is central to early axon patterning and organization, thereby influencing network excitability. We are also developing novel AIS targeted inhibitory opsins to examine whether we can replace GABAergic signaling to the AIS in early development to rescue AIS morphology and seizure susceptibility. These studies are expected to increase understanding of the intersecting mechanisms mediating developmental susceptibility to seizures, with implications for new therapeutic strategies in the treatment of developmental epilepsies.

Quantifying dendritic chloride microdomains in cytotoxic edema using fluorescence lifetime imaging

Nicholas Weilinger[1], Jeffrey LeDue[1], Kristopher Kahle[2], Brian MacVicar[1]

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BACKGROUND AND AIM: Chloride (Cl-) homeostasis is pivotal to healthy neurotransmission but also volume regulation as a key determinant of cytosolic tonicity. As such, Cl- gradients across the neuronal plasmalemma are tightly constrained to preserve inhibitory tone and cell volume, rendering it difficult to manipulate intracellular Cl- concentration ([Cl-]i) by whole-cell patch clamp. We are combining electrophysiology with fluorescent lifetime imaging (FLIM) to quantify the intrinsic variability of [Cl-]i within cells. We asked how the subcellular [Cl-]i distribution was influenced by excitatory activity to glean insights into Cl- influx and cellular swelling (cytotoxic edema). METHODS: Layer 4 pyramidal neurons were whole-cell patch-filled with the Cl- sensitive dye MQAE, enabling us to map the spatiotemporal shifts in [Cl-]i and commensurate changes in dendritic volume. RESULTS: Patched neurons maintained dendritic (but not somatic) [Cl-]i at baseline levels by homeostatic K+/Cl- cotransporter (KCC2) Cl- efflux despite dialysis of the recording solution. Challenging cells with an elevated (80 mM) [Cl-]i load by whole-cell dialysis revealed nonuniform Cl- subdomains in the dendritic arbour. Depolarization increased [Cl-]i and was exacerbated by blocking KCC2 with furosemide. In contrast to depolarization alone, NMDA application elicited significant Cl- entry upwards of 70 mM from rest (~10 mM) and dendritic beading. Under these conditions, dramatic subcellular [Cl-]i heterogeneities were observed along dendritic shafts/spines, with severe beading occurring in regions where [Cl-]i was highest. CONCLUSIONS: We conclude that dendritic [Cl-]i is stabilized at rest in patched neurons and is overwhelmed by NMDA activation, revealing distinct Cl- microdomains that couple directly to membrane beading.

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Parallel symposium 5: Dopamine and the response to environmental variation over the lifecourse: Clinical, neuroimaging, genomic and context characterization studies

Presenters: Laurette Dube, McGill University (Chair); Robert D. Levitan, CAMH; Susan Carnell, Johns Hopkins Medical Institute; Cecilia Flores, McGill University; Patricia Silveira, McGill University

Chaired by L. Dube, this symposium examines multiscale brain-to-society mechanisms modulating the effect of dopamine on responsiveness to environmental variations over the lifecourse. R.Levitan will discuss the possible evolutionary and clinical significance of linkages between the 7R allele on the DRD4 gene and increased environmental sensitivity in adults with seasonal affective disorder and bulimia nervosa, as well as in young children's response to maternal sensitivity. S. Carnell will report neuroimaging results in adolescents, tracing structure and function of obesity-relevant circuits underlying dopamine-mediated food and non-food behaviors, while addressing genetic and environmental modulations. C. Flores will report animal research on developmental aspects of the dopaminergic system, discussing the role of axonal guidance cues on stress adaptation and its long-term effects in adolescence. B. Barth and L. Dube will present research advancing both the characterization of adverse and protective environmental variations over the lifecourse, and genomic methods to explore their interaction with dopamine-related genes on the brain responses.

DRD4, Environmental Sensitivity and Weight Gain across the Atypical spectrum of Mood Disorders: A Lifespan Perspective

Robert Levitan[1]

[1]*CAMH, University of Toronto*

The atypical spectrum of mood disorders includes a variety of phenotypes characterized by unusually high sensitivity to environmental factors as well as increased eating behaviour and weight gain. In the case of Seasonal Affective Disorder, the environmental sensitivity relates to highly predictable photoperiodic phenomena tied to the seasons of the year. In the case of DSM-defined atypical depression, the environmental sensitivity relates to the social realm as reflected in the construct of rejection sensitivity. Patients with various forms of binge eating are highly sensitive to both appetitive and non-appetitive stimuli over time. Our group has been interested in identifying gene-environment interactions that might explain why certain individuals are more prone to develop these disorders characterized by environmental sensitivity and overeating/weight gain. Our primary genetic focus has been on the seven-repeat allele (7R) of the DRD4 gene because it is a hypo-functional variant that is likely to influence dopamine system functioning over the lifespan. There is also significant evidence that the 7R allele moderates phenotypic development in the face of various environmental signals. The current talk will review various findings linking the 7R allele to increased environmental sensitivity in patients with Seasonal Affective Disorder, bulimia nervosa and to young children exposed to various levels of maternal sensitivity in the early postnatal period. The possible evolutionary and clinical significance of these findings will also be discussed.

Neural correlates of dopamine-related obesogenic behaviors in early and later development: human MRI studies

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Susan Carnell[1]

[1]*Johns Hopkins University School of Medicine*

We all inhabit an 'obesogenic' environment, yet not everyone becomes obese. This may be in part because individuals differ systematically in dopamine-mediated behaviors that begin to influence body weight as early as infancy. These behaviors include food cue responsiveness, i.e. the degree to which exposure to environmental food cues triggers overconsumption. A significant body of work using standardized behavioral tests and validated questionnaires suggests that food cue responsiveness tracks through development, predicts adiposity, and is influenced by genetic as well as environmental factors. Neuroimaging studies have begun to establish the network of subcortical and cortical brain regions playing a role in human appetite. But much is still to be learnt about the circuits subserving specific dimensions of appetite observed in behavioral studies of children, including food cue responsiveness. In MRI studies of adolescents, children and infants, we are using tasks eliciting neural responses to food cues, as well as measures of brain structure and resting state connectivity, to investigate circuits underlying obesity-relevant behaviors encompassing food and non-food related reward, and food and non-food related inhibitory control, and how their structure and function change with development and are impacted by genetic and environmental factors. This talk will review established and preliminary results from this program of research and outline potential future directions to elucidate the role of dopamine in determining individuals' behavioral responses to the obesogenic environment.

Stress in adolescence alters guidance cue pathways and impacts dopamine development

Cecilia Flores[1]

[1]*McGill University*

Dopamine (DA) connectivity in the prefrontal cortex (PFC) continues to unfold until early adulthood, with dramatic organizational and functional changes occurring during adolescence. This delayed development involves long-distance axonal growth of midbrain DA neurons across the adolescent period and is mediated by the Netrin-1/DCC guidance cue pathway. We examined whether repeated social stress in adolescence dysregulates the Netrin-1/DCC pathway, disrupting PFC DA innervation and cognitive control in adulthood. We used a modified accelerated social defeat stress (ASD) model and segregated mice into resilient (RES) and susceptible (SUS) groups by measuring social avoidance in a social interaction test (SIT) 24h after ASD exposure. ASD in adolescence downregulates DCC expression in DA neurons in SUS and RES groups, but its effects on PFC DA development and behavior differ between phenotypes. ASD-induced molecular, cellular and behavioral changes are not observed following ASD exposure in adulthood. While most (~60%) mice exposed to adolescent ASD show RES, most adult mice show stress SUS. Alterations in dopamine development in adolescence may mediate the established link between genetic variance within the Netrin-1/DCC pathway and psychiatric disorders of neurodevelopmental origin.

The role of dopamine on the link between early life environment and lifecourse eating behavior and co-morbidity between metabolic and psychiatric disorders: Context characterization and biologically-informed genomic approaches

Barbara Barth[1]*, Patricia Silveira*[1]

[1]*McGill University*

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Individual differences in dopamine gene and brain systems influence the responsiveness to environmental variations and affect different types of behaviors (sensitivity to reward, decision-making, eating) over the life course. Robust evidence points to DRD4 gene but neither the characterization of context diversity and dynamics, nor the neurobiological mechanisms involved in metabolic disorders and their co-morbidity with psychiatric conditions (e.g. obesity and ADHD) are understood in sufficient depth. Evidence advancing the theoretical understanding of environmental variation characterization over the life course will first be presented. Second, studies focusing on different genomic approaches to explore the impact of variations of dopamine related genes on the brain responses to both adverse and protective environmental conditions. A recent published study that explored differential susceptibility to positive environments according to the predicted genetically-regulated gene expression of prefrontal cortex DRD4 gene will be presented, evidencing the role of positive environment as a protective factor against the development of eating disorders in children as young as 48 and 60 months of age. To be able to further investigate the role of dopamine on these gene by environment interactions, we will present new data exploring the role of the dopamine transporter gene network through a polygenic approach that reflects variation on the genes co-expressed with DAT1 gene in the PFC and STR in a combined manner. A higher chance of having co-morbidity between mental and cardio-metabolic disorders on the UKBiobank cohort was associated with the interaction between variations in the DAT1 gene network and exposure to early life adversity, confirming our initial hypothesis. Taken together these findings highlight the relevance of a dopamine-related gene network to influence the risk to develop psychiatric conditions associated with exposure to early life adversity. Combining this novel approach to developmental neuropsychology with a more theoretically rich characterization of environmental variation over the life course can guide the elaboration of more efficacious and cost-effective personalized prevention and treatment of complex metabolic and mental health and diseases, targeting individuals that would benefit the most from interventions.

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Parallel symposium 6: The ever expanding roles of astrocytes in neural circuits, metabolism and disease

Presenters: Angela Scott, McMaster University (Chair); Grant Gordon, University of Calgary; Jillian Stobart, University of Manitoba; Arlette Kolta, Université de Montréal

There are many areas of research strengths in Canadian neuroscience, and as a newer faculty member, I am excited by the significant rise of excellent research focused on glial cells. Please accept this proposed symposia that is designed to highlight work pertaining directly to the roles of astrocytes in both normal conditions and disease states for this upcoming CAN meeting. In particular, we will have topics that explore role of astrocytes: in modulating circuit firing in the somatosensory system; in regulating brain blood flow and the delivery of oxygen and glucose to active regions; in driving abnormal hyper-excitability of sensory afferents and underlying pain; and finally how the dysregulation of astrocyte-secreted factors contributes to neurodevelopment disorders. I believe this a good mix between examination of normal and abnormal conditions, which are highly related yet also representative of the various roles astrocytes can play. This symposia would highlight Canadian researchers, 3/4 women, and all at different career stages. The glial field is continually growing globally and it would be wonderful to have good representation of that at CAN.

Dysregulation of astrocyte-mediated purinergic signalling leads to atypical neuronal development in Fragile X Syndrome

Kathryn Reynolds[1], Gregory Vandenberg[1], Chloe Wong[1], Shirley Andrews[1], Angela Scott[1]

[1]McMaster University

BACKGROUND AND AIM: Neural communication and the intricate choreography of signals required for the formation and preservation of neural connections is heavily dependent on reciprocal neuronal and glial interactions. Astrocytes are key participants in neurodevelopmental processes and defects to astrocyte signalling are implicated in many disease states such as Fragile X Syndrome (FXS), the leading monogenetic cause of intellectual disability and autism. In FXS, the loss of the Fragile X mental retardation protein (FMRP) from astrocytes is associated with improper synapse formation and circuitry activity. During development purinergic signalling is one of the predominant intercellular means of communication in the brain; however, how this signalling system functions in neurodevelopmental disorders is unknown. Here, we aimed to uncover the molecular mechanisms of atypical glial-neuronal interactions in FXS and determine the potential role of purinergic signalling. METHODS: We examined the physiological responses of astrocytes, isolated from either postnatal wild-type (WT) mice or transgenic fmr1 knockout (KO) mice, to exogenous purinergic stimulation and antagonism. In addition, we compared WT and KO purinergic receptor levels, synaptic factor regulation, neuronal growth and circuitry development using a variety of in vitro and in vivo assays. RESULTS: Intracellular calcium measurements revealed greater activation of KO astrocytes in response to ATP (and UTP) due to increased expression of purinergic receptors (P2) in comparison to wildtype (WT) counterparts. Abnormal astrocyte activity also led to enhanced levels of reactive oxygen species and possible oxidative stress. Pharmacological targeting of purine-mediated signalling corrected astrocyte hyperactivity, prevented aberrant expression of synaptic factors, and modified neuronal growth in the FXS model. CONCLUSIONS: Our work suggests that targeting the purinergic system could be an effective therapeutic approach to normalize aberrant glial-neuronal interactions in FXS and potentially other neurodevelopmental disorders.

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Bidirectional communication between astrocytes and arterioles controls vasomotion

Grant Gordon[1]

[1]*University of Calgary*

The resting perfusion of blood to the brain is immense and essential for proper function yet we have little understanding of how the brain regulates its basal blood supply. Astrocyte-mediated neurovascular coupling has conventionally been examined in the context of transient neuronally-evoked calcium (Ca2+) events triggering phasic changes in arteriole diameter to control blood flow. However, our group recently demonstrated that "resting" astrocyte Ca2+ levels control tonic, neural activity independent, brain blood flow. It was unclear if or how fluctuations in resting astrocyte Ca2+ regulated vascular tone in vivo. Using two-photon fluorescence imaging, astrocyte patch-clamp, pharmacology, chemogenetics and cre-lox gene knockdown in acute cortical brain slices and in vivo, we showed that increases in arteriole tone (vasoconstriction) caused a sustained elevation in the astrocyte endfoot Ca2+ level. Pharmacology suggested that a TRPV4-mediated Ca2+ influx initiated a Ca2+-dependent COX-1 pathway in endfeet that triggered the release of prostaglandin vasodilators. The role of endfoot COX-1 was further demonstrated with astrocyte specific cre-lox knockdown of the COX-1 gene PTGS1. Furthermore, chemogenetic control of arteriole constriction was sufficient to engage this pathway. While in brain slices this pathway appeared to be a static effect on arteriole tone, in awake mice in vivo, we found this pathway was involved in vasomotion - a pulsatile phenomenon of vascular contraction and relaxation occurring at ~0.1Hz which is important for the basal perfusion of tissue. Using an astrocyte selective AAV to overexpress a Ca2+ extrusion pump called CalEx, which clamps astrocyte free Ca2+ at a lower level and prevents increases, this largely abolished vasomotion compared to control virus. Our data demonstrated that bidirectional communication between astrocyte endfeet and arterioles is important for setting basal arteriole tone and vasomotion in vivo, which is likely an essential process for optimizing cerebral perfusion of oxygenated blood.

Astrocyte integration into cortical circuits through microdomain calcium events

Jillian Stobart[1]

[1]*University of Manitoba*

BACKGROUND AND AIM: In the cortex, astrocytes are densely packed with receptors and ion channels that induce localized, heterogeneous intracellular calcium transients, termed microdomain calcium events. These calcium events occur spontaneously, but also in response to sensory stimulation, effectively incorporating astrocytes into cortical circuits. This is important because astrocyte calcium events are believed to be required for various astrocyte functions, including release of gliotransmitters and changes in metabolism relating to astrocyte support of neuronal energy expenditure. Thus, astrocytes may modulate neuronal activity following microdomain calcium events. However, this remains to be proven in the cortex and further characterization of cortical astrocyte signalling is needed. METHODS: We used novel combinations of genetically encoded calcium indicators (Lck-GCaMP6f and RCaMP1.07) for concurrent two-photon imaging of cortical astrocytes and neurons in awake mice during single whisker vibrotactile stimulation. RESULTS: We identified calcium responses in both astrocyte processes and endfeet near blood vessels that rapidly followed neuronal calcium events. These fast astrocyte microdomains were independent of local neuromodulator activity and second messenger signalling for calcium release from endoplasmic reticulum. We also disrupted astrocyte NMDA receptor expression and found that this perturbed astrocyte microdomain calcium events and normal neuronal activity evoked by

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sensory stimulation. CONCLUSIONS: Our work suggests that astrocytes are integrated into neuromodulatory and glutamatergic circuits of the cortex where they can influence neuronal activity. This opens exciting new avenues into an astrocytic role in cortical information processing.

Astroglial modulation of neuronal firing pattern in cortical and brainstem sensorimotor circuits

Arlette Kolta[1]

[1]*University of Montreal*

BACKGROUND AND AIM Several functions, motor or sensory, rely on the ability of neurons to modify their discharge pattern to faithfully encode the characteristics of a sensory stimulus or to reflect a rhythmic motor control for example. Changes in firing pattern often involve particular ion channels and are intimately related to the function of the circuit. Astrocytes are increasingly recognized as key regulators of neural activity, through release of gliotransmitters. An increasing number of studies have documented how they affect synaptic and network functions. However, their contribution to neuronal computations is still poorly understood. METHODS: Whole cell patch recordings of neurons and astrocytes was combined to Ca2+-imaging and optogenetic manipulations in either brainstem or cortical slices from rats and transgenic mice. RESULTS: Here I will describe a mechanism first identified in a brainstem trigeminal circuit where neuronal firing pattern depends on particular Na+ channels sensitive to the extracellular Ca2 + concentration which is regulated by astrocytes through release of the calcium-binding protein, S100ß. The same mechanism also contribute to inputs integration and influences the input-output function of cortical layer 5 pyramidal neurons, and of primary afferents neurons. I will also describe how astrocytic coupling define functional domains and determines synchronization and coordination of neuronal firing within these domains. CONCLUSIONS Neuron-glia interactions are most often thought to occur at or near synapses. Our results suggest that astrocytes control neural activity by acting directly on or near the neuronal ionic channels, a largely unexplored form of communication between astrocytes and neurons. The S100β-dependent mechanism adds up to the previously reported conventional gliotransmitters such as glutamate, GABA, and ATP. Beyond increasing our understanding of how astrocytes contribute to neuronal computations an important value of our findings resides in the increased understanding of the role of S100β which is abnormally regulated after trauma and in many neurological disorders including epilepsy, depression, Parkinson's and Alzheimer's diseases. We propose that abnormal S100β control may have a wide impact by leading to abnormal extracellular ionic environment, abnormal neural activities, and thus pathological states.

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Poster Session 1

A – Development

1-A-1: Cortical layer distribution of SOX9+ astrocytes from V-SVZ neural stem/progenitor cells depends on time of birth

Ines Kortebi[1], Tanvi Sharma[1], Daniela Lozano-Casasbuenas[1], Arman Olfat[1], Emerson Daniele[1], Maryam Faiz[1]

[1]University of Toronto

Cortical astrocytes are highly heterogeneous cells with distinct gene expression profiles, phenotypes, and functions. They are born from neural stem/progenitor cells (NSPCs) during embryonic development starting at E15 and undergo a period of rapid expansion in the first postnatal week. Whether time of astrocyte birth from NSPCs determines their position within the murine cerebral cortex is not known. To determine whether time of birth influences astrocyte distribution in the upper (UL) vs. lower (LL) cortical layers, we permanently labelled ventricular-subventricular zone (V-SVZ) NSPCs and their progeny via in utero electroporation with PiggyBac (PB)-CAG-EGFP at E15, 16, and 17 and sacrificed animals at P21. Immunohistochemistry (IHC) for the astrocyte lineage marker SOX9 was performed and EGFP+SOX9+ or EdU+SOX9+ astrocytes were quantified and compared between UL and LL cortical layers within each timepoint. PB-based labelling of EGFP+SOX9+ astrocytes showed that E15- and E16-born astrocytes were mostly found in the UL at P21; this bias was lost in E17-born astrocytes. As an alternative birth dating method, 5-ethynyl-2'deoxyuridine (EdU) was administered to pregnant mice at E16 and tissue was collected at P3 prior to astrocyte expansion. EdU labelling confirmed that SOX9+ astrocytes born at E16 were mostly found in the UL at P3. Altogether, our results suggest that the distribution of SOX9+ cortical astrocytes is influenced by birth date.

1-A-2: Increased expression of Ehmt1/GLP protein in embryonal neurogenesis, and specific postnatal and adult mouse and rat brain neurogenesis areas

Catharina Van der Zee[1], Hans van Bokhoven[2]

[1]Radboudumc, [2]Radboud University Medical Centre

Euchromatin histone methyltransferase 1 (Ehmt1) is a protein which regulates transcription by catalyzing methylation of histones, which then can lead to silencing of gene expression. Haploinsufficiency of the EHMT1 gene, with only 1 functional allele for the Ehmt1/GLP protein, results in humans in a congenital intellectual disability syndrome called Kleefstra Syndrome. Mice with a heterozygous mutation for Ehmt1 (Ehmt1+/-) proved to be an excellent animal model to study Kleefstra Syndrome (Balemans et al. 2010, 2013, 2014 and Iacono et al. 2018). Balemans et al. (2013) showed for Ehmt1+/- mice that Ehmt1 protein levels in brain cortex, hippocampus, cerebellum and olfactory bulb are 50% lower than levels measured in littermate wildtype mice, using quantitative Western Blot analysis. In this study, we focused on wildtype brain and demonstrated Ehmt1 protein expression in all cells in all parts of mouse and rat brain. Notably, embryonal stage shows high expression, in the postnatal phase the expression decreases, and in adult brain there is a lower, but apparent

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Ehmt1 protein expression. Interestingly, significantly elevated Ehmt1 protein levels were found in the two known adult rodent neurogenesis areas: the Dentate Gyrus Subgranular layer and the subventricular zone-RMS-Olfactory bulb areas. A correlation between the number of darkly stained Ehmt1-positive cells and the number of DCX-positive cells in the dentate gyrus subgranular layer and in the subventricular zone / RMS indicates a role for Ehmt1 in adult neurogenesis.

1-A-3: Early adversity modifies physical, sensory and motor neurodevelopmental milestones in rat pups.

Annie Phan[1], Hong Long[2], Claire-Dominique Walker[2]

[1]McGill University and Douglas Institute Research Center, [2]McGill University

Exposure to early life stress in humans and animals confers long-term consequences, affecting brain structure and function and increasing the risk for neuropsychiatric pathology. Early life stress can take different forms, such as parental loss, abuse, or poverty. The limited bedding (LB) paradigm has been used in animal models to simulate stress related to the lack of resources, affecting maternal care of her offspring. However, it is still unclear how the LB paradigm affects neonatal brain development, whether the reaching of specific neurodevelopmental milestones is modified differently in male and female offspring and whether a specific domain is preferentially affected. We examined daily reaching of physical, sensory, and motor milestones between P1-15 in offspring from LB and normal bedding (NB) mothers. We later tested open field locomotion and conditioned fear learning using the same animals as juveniles (P28). Animals subjected to the LB condition showed significant delays in achieving physical milestones, such as auditory canal opening; sensory milestones, such as ear twitching reflex and auditory startle response; and motor milestones, such as grasping reflex and surface righting reflex, compared to NB animals. Sex had no significant effect on some of these delays. At the juvenile stage, locomotor activity and conditioned fear response were comparable between groups and sex, suggesting that some of the maturational delays were compensated for after weaning for at least some behaviors. Supported by CIHR PJT162376 to CDW.

1-A-4: Effects of nicotine vapour exposure on reward and withdrawal in adolescent and adult rats

Jude Frie[1], Ahmad Hassan[1], Karling Luciani[1], Chuyun (Judy) Chen[1], Jaiden Smith[1], Bryana Hallam[1], Jibran Khokhar[1]

[1]University of Guelph

Aim: Youth nicotine exposure is a continued concern due to the growing use of electronic cigarettes and their largely unknown addiction liability, especially during vulnerable periods such as adolescence. Thus, the aim of the following research is to assess developmental differences in nicotine vapour-associated reward and withdrawal. Methods: Experiment 1 - adult and adolescent rats (n = 5-6/group) were exposed to either nicotine (JUUL, 5% nicotine) or vehicle (30:70 propylene glycol to glycerol) vapour using the open-source vapour exposure apparatus, OpenVape, for 10 minutes at 3 doses (2, 4, or 8 minutes of active vapour puffs). To evaluate the reward-like properties of nicotine, a biased place conditioning paradigm was implemented. Experiment 2 - adult and adolescent rats of both sexes (n = 7-8/group) were exposed to either JUUL or vehicle vapour for 10 minutes 3 times

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a day for 2 weeks. 16 hours following their final exposure, rats were injected with 1.5 mg/kg mecamylamine. 20 minutes following injections, rats were scored for somatic signs of withdrawal for a period of 10 minutes. Results: Experiment 1 - Two-Way ANOVA revealed a significant effect of age ($F(1,45) = 9.872$, $p < 0.003$) and dose ($F(3,45) = 7.098$ $p < 0.001$). Both adult and adolescent male rats showed significant increases in place preference for the nicotine-paired side, with adolescents displaying significant increases at lower doses than adults. Experiment 2 - Three-Way ANOVA revealed a significant effect of treatment ($F(1,51) = 15.99$, $p < 0.0002$) and Sex ($F(1,51) = 15.91$, $p < 0.002$) but not age ($F(1,51) = 1.151$, $p = 0.2880$). Conclusions: Our results support the notion that adolescence is a period that is more sensitive to the rewarding effects of, but not withdrawal from, nicotine.

1-A-5: A subpopulation of embryonic microglia respond to maternal stress and influence nearby neural progenitors in a sexually dimorphic manner

Jessica Rosin[1], Sarthak Sinha[1], Jeff Biernaskie[1], Deborah Kurrasch[1]

[1]University of Calgary

Microglia are the resident macrophages and phagocytic immune cells of the central nervous system (CNS). We were interested in whether unique clusters of microglia existed in the embryonic hypothalamus, since the hypothalamus controls a variety of physiologies important for proper body homeostasis. Using single-cell transcriptomics, we identified four distinct populations of microglia within the embryonic hypothalamus, including a subpopulation of microglia with unique expression signatures that were in direct contact with neural stem cells (NSCs). Considering the proximity of this microglial subpopulation to developing hypothalamic stress-responsive neurons in the paraventricular (PVN), we asked whether these microglia reacted to maternal challenge, specifically temperature stress. Indeed, maternal cold stress elevated the number of these microglia during embryogenesis and resulted in both decreased numbers of oxytocin neurons in the PVN and decreased numbers of oligodendrocyte precursor cells (OPCs) in the hypothalamus of male embryos. These sexually dimorphic findings correlated with an elevation in CCL3 and CCL4 secretion, and ex vivo CCL4 treatment of hypothalamic NSCs altered proliferation and differentiation. Moreover, gestational cold stress led to altered social behaviours in adulthood, while depleting microglia only blocked the development of these adverse behaviours in males. Together, these important findings demonstrate that embryonic microglia might play an unappreciated role in translating maternal stressors to perturbations in the developing brain.

1-A-6: Lactic-acid probiotics enhance glucose tolerance and weight gain in a pubertal mouse model

Michael Murack[1], Zachary Lazaridis[1], Naghmeh Nikpoor[2], Thomas Tompkins[2], Claude Messier[1], Nafissa Ismail[1]

[1]University of Ottawa, [2]Lallemand Inc.

Puberty is a critical period of sexual maturation that is vulnerable to the development of metabolic disorders. Metabolic disorders like Type-1 diabetes are more likely to develop in youths near the onset of puberty. Diabetes onset occurs later in boys than girls, mirroring average sex differences in pubertal onset. Attempts to control diabetic symptoms at their onset may improve prognosis and disease management. Lactate-producing probiotics improve glucose tolerance in adults, but it is unclear if this effect extends to pubertal

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individuals. Administration of lactate-producing probiotics may assist with glucose management at a vulnerable period of metabolic development. As of 5 weeks of age, 80 male and female CD-1 mice were given ad libitum access to either a control broth, or one of two probiotic solutions (Lacidofil or Cerebiome) for 14 days. Lacidofil and Cerebiome are proprietary blends of Lacticaseibacillus rhamnosus, Lactobacillus helveticus, and Bifidobacterium longum. Weight change and blood glucose and L-lactate concentrations were assessed with an oral glucose tolerance test prior to and after the probiotic treatment period. Pubertal male and female mice displayed less blood glucose, weight gain, and more blood L-lactate after Lacidofil treatment. Pubertal female mice displayed significantly less blood glucose, weight gain and more blood L-lactate after Cerebiome treatment. Our findings indicate that lactate-producing probiotics improve glucose tolerance in mice in a sex-specific manner and may assist in managing metabolic impairments consistent with diabetic development in pubertal groups.

1-A-7: Fractalkine receptor deficiency impairs behavioural, hippocampal, and microglial responsiveness to maternal immune activation in adult mouse offspring

Micaël Carrier[1], Chin Hui[2], Imene Melki[1], Eva Simoncicova[1], Valerie Watters[2], Katherine Picard[1], Fernando Gonzalez Ibanez[1], Nathalie Vernoux[2], Arnaud Droit[2], Marie-Ève Tremblay[1]

[1]University of Victoria, [2]Université Laval

Microglial functions were found to be altered in many neurodevelopmental disorders including schizophrenia. Previous work by our group showed sex-specific alterations of microglia and synapses in adult mouse offspring exposed to maternal immune activation (MIA) induced with polyinosinic:polycytidylic acid. To provide further insight into the role of microglia in MIA, we studied its outcomes in fractalkine receptor (CX3CR1) knockout (KO) mice, in which neuron-microglia communication via fractalkine (CX3CL1)-CX3CR1 signaling is impaired. MIA caused an obsessive type of behavioural deficit in wild-type mice, which was not observed in CX3CR1 KO mice. Microglial density, morphology, and phagolysosomal activity were further assessed in the hippocampus by confocal microscopy, with no difference observed following MIA, in both genotypes. However, RNA sequencing and pathway enrichment analysis in whole hippocampus revealed differences between the CX3CR1 KO and wild-type mice exposed or not to MIA. For instance, in the wild-type mice exposed to MIA, female offspring displayed an increase in immune related pathways, while males showed altered organ development and DNA expression related pathway. Our finding supports the evidence that fractalkine signaling is linked to cognitive deficits upon MIA, consistent with findings of rare gene variants of CX3CR1 disrupting its signaling notably in schizophrenia patients. Neuroimmune communication is emerging as important for the development of neurodevelopmental disorders, suggesting therapeutic avenues targeting the neuron-microglia crosstalk.

1-A-8: Regulation of neural stem cell fate by a novel PHF6/EphR transcriptional pathway

Dilan Rasool[1], Audrey Burban[1], Ahmad Sharanek[1], Vahab Soleimani[1], Azad Bonni[2], Hamed Najafabadi[1], Arezu Jahani-Asl[1]

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PHF6 is a transcriptional regulator with its germline mutations causing the X-linked intellectual disability BFLS, a congenital neurodevelopmental disorder (Jahani-Asl et al., 2016). The precise mechanisms by which PHF6 regulates transcription, and its mutation causing BFLS and cognition deficits remain poorly understood. Here, we employed next generation sequencing platforms, including ChIP-Seq and RNA-Seq, to gain mechanistic insights into PHF6 function. We identified 2473 PHF6 binding sites, with regions significantly overlapping (CA)n-microsatellite repeats enriched near genes involved in developmental processes, including central nervous system development and neurogenesis. Through intersection of ChIP-Seq and RNA-Seq data, we found that PHF6 binding to the TSS inhibits Pol II recruitment and inhibits expression, whereas PHF6 binding further downstream of the TSS increases expression. Importantly, we identified a large panel of Ephrin receptors as direct target genes of PHF6. Through luciferase reporter assay and ChIP-PCR, we found that PHF6 occupies and binds the promotors of EphR genes. Additionally, we observed a decrease in EphR expression in BFLS mouse models. Furthermore, we found that mice harboring a BFLS mutation exhibited an increase in eNSC numbers measured by expression of stem cell markers, Sox2 and Nestin, as well as increased self-renewal measured by ELDA/LDA self-renewal assays. In conclusion, we established that a novel PHF6/EphR transcriptional pathway may regulate neurogenesis, and impairment of this pathway may lead to the pathogenesis of BFLS.

1-A-9: Prenatal PGE2 exposure causes abnormal cerebellar dendritic morphology and cerebellar related motor coordination in mice

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Background: ProstaglandinE2 (PGE2) is a lipid signalling molecule involved in healthy neurodevelopment. Abnormal PGE2 levels due to genetic or environmental factors are linked to autism spectrum disorders (ASD). Our lab has shown that maternal PGE2 exposure results in differential developmental gene expression, and autism-like behaviours in offspring, including social deficits, and repetitive and anxious behaviours. Our goal was to examine the sex-dependent effect of prenatal PGE2 exposure on cerebellar dendritic morphology and related motor coordination. Methods: Cerebellums of PGE2 and Saline-injected C57BL/6 (WT) offspring at postnatal day 30 were stained with the GOLGI-COX method to measure dendrite length, branching, and the odds of observing dendritic loops. We also examined cerebellar-related motor function using adhesive sticker, grid walking, and cylinder tests. Results: PGE2 mice (males and females) had greater dendritic arborization closer to the soma and higher odds of observing dendritic loops than WT controls. Dendrite length was greater in WT Females (WTF) than in Males (WTM) with no significant differences observed in PGE2 Males (PGE2M) and Females (PGE2F). In the adhesive sticker test, we saw no significant differences in first sticker removal attempt times but more attempts per second in PGE2M. In the grid walking test, PGE2M slipped through the grid more than PGE2F, despite no WT sex differences. While WTM escaped faster than WTF, PGE2M escaped slower than PGE2F. In the cylinder test sex differences in rearing and wall touching in WT mice were lost in PGE2 mice. We saw a reduction in steps in PGE2M compared to WTM. We show that prenatal PGE2 signalling disruptions result in sex-dependent abnormalities in cerebellar development and behaviour.

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1-A-10: The impact of impaired cyclooxygenase-2 activity during mouse brain development: a focus on sex differences

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There is a clear male bias in the prevalence of neurodevelopmental disorders (NDDs). Certain environmental factors have been shown to contribute to the etiology of these NDDs, including exposure to antipyretic drugs. To investigate the molecular mechanisms by which environmental factors may contribute to the male bias in NDDs, we focused on two genetic models that mimic antipyretic drug exposure, namely cyclooxygenase-2 knockin (COX-2-) and COX-2 knockout (COX-2-/-) mice. Illumina and Affymetrix GeneChip arrays were used to profile gene expression in brain samples obtained from COX-2-/- mice during prenatal development. Impaired COX-2 activity was found to downregulate the expression of various neuroimmune markers in the brain of males, whereas markers of ribosomal activity were upregulated in females. Further investigations using Real-Time qPCR on postnatal brain samples also revealed that gene markers linked to distinct subtypes of astrocytes were dysregulated in male and female COX-2- mice. While males exhibited an increased prevalence of neurotoxic A1 astrocytes, females exhibited an increased prevalence of neuroprotective A2 astrocytes. Our findings offer novel insight into the sex-dependent effects of antipyretic drugs, which may ultimately facilitate the discovery of therapeutic targets for NDDs exhibiting a male bias.

1-A-11: Key elements of rehabilitation pathway for impaired attention after traumatic brain injury in Korea

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Purpose:Impaired attention is the most common and debilitating cognitive deficit following traumatic brain injury (TBI), leading to rehabilitation barriers and long-term disability. Few studies have explored a standardized and evidence-based rehabilitation pathway for impaired attention after TBI. The aim of this study was to gather expert opinion and identify key elements of rehabilitation pathway for attention deficits after TBI. Methods: First, a survey was conducted among 49 rehabilitation experts from designating teaching hospitals to identify the priority in developing the pathway. Second, evidence and priority-based elements of the pathway were set up for acute and post-acute TBI patients. Thirdly, content validity was evaluated by the Modified Delphi technique on 16 neurorehabilitation professionals. Finally, a qualitative study was conducted, using a focus group interview. Results: 'Successful return to the community' and 'development and dissemination of an attention rehabilitation manual' were academic issues of the highest priority in terms of importance and urgency, respectively. Elements of acute pathway included classification of TBI severity, history and physical exam, clinical testing, assessment and management of postconcussion symptoms and neuropsychiatric sequelae in mild TBI, and disorder of consciousness and post-traumatic confusional state in moderate to severe TBI, cognitive rehabilitation, and outcomes. The post-ac pathway highlighted comprehensive and evidence-

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based assessment, cognitive rehabilitation programs, medication, and education. Conclusion: Implementation of the rehabilitation pathway for attention impairment after TBI may improve a physiatrists' practice and patients' outcome by decreasing the clinical variances, length of hospi

1-A-12: Maternal exposure to prostaglandin E2 affects hippocampal dendritic morphology in C57bl/6 mice offspring - link to autism spectrum disorder (ASD)

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Background: Prostaglandin E2 (PGE2) is a bioactive lipid molecule involved in healthy brain development, including neuronal differentiation, migration and plasticity. Exposure to various environmental factors during pregnancy such as infections, inflammation, acetaminophen or misoprostol leads to abnormal PGE2 levels and has been linked to Autism Spectrum Disorders (ASD). We have previously determined that maternal exposure to PGE2 results in differential expression of developmental genes and associated autism-like behaviours, including social and motor deficits, repetitive and anxious behaviours. This study investigates sex-dependent effects of a maternal PGE2-exposure at embryonic day 11 (E11) on the morphology of dendrites of C57bl/6 mice offspring. Methods: The hippocampi of PGE2 and Saline-injected wildtype (WT) male and female offspring at postnatal day 30 were stained using the Golgi-Cox method, followed by confocal microscopy to examine dendritic arborization, length, branch order and the odds of observing dendritic loops. Results: We show that compared to matched WT controls PGE2-exposed males and females (PGE2M and PGE2F) had a statistically greater dendritic arborization closer to the soma, had greater primary branching and increased odds of observing dendritic loops. Also, dendrite length was greater only in PGE2M, compared to the controls. Overall, this study provides new evidence that single maternal PGE2 exposure during the critical time in prenatal development contributes to sex-dependent changes in dendritic architecture in the hippocampus of offspring.

1-A-13: A mesocorticolimbic dopamine gene network moderates the effect of early adversity on the risk for metabolic and psychiatric comorbidities

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Exposure to early adversity increases the risk for non-transmittable diseases, but also psychiatric conditions, and these common developmental risk factors suggest overlapping underlying mechanisms. The dopamine neurons constitute a system underlying the brain response to environmental conditions and functional variations of this system may be linked to long-term unfavorable outcomes in response to early adversity. We created an expression-based polygenic score for the dopamine transporter gene network (ePRS-DAT1) on the prefrontal cortex and striatum, to explore the role of dopamine on the long-term effects of early life adversity on these outcomes. The ePRS-DAT1 reflects genes co-expressed with DAT1 gene in the PFC and STR in a combined manner, being calculated

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using the effect size of the association between the individual SNPs from those genes and gene expression (GTEx). Using large datasets (UKBiobank for adulthood and ALSPAC for childhood/adolescence), we demonstrate that the ePRS-DAT1 moderates the impact of early life adversity on the risk for both psychiatric and cardiometabolic comorbidities in adults and adolescents. Brain gray matter densities in the insula and prefrontal cortex were significantly associated with SNPs from the ePRS suggesting these regions as critical dopaminergic targets for psychiatric/metabolic comorbidities. These results reveal that psychiatric and metabolic comorbidities showed share common developmental pathways and underlying biological mechanisms.

B - Neural Excitability, Synapses, and Glia: Cellular Mechanisms

1-B-14: Cyclic AMP influences electrotonic transmission between coupled neuroendocrine cells

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[1]Queen's University

Neuronal synchrony is often achieved by electrical synapses, which are mediated by intercellular channels, known as gap junctions. Electrical transmission can be modulated by intracellular pathways, including direct effects on connexins/innexins, the pore forming subunits of gap junctions, or alterations to the electrical properties of the postsynaptic neuron. Reproduction in the sea snail, Aplysia, is controlled by electrically coupled bag cell neurons. Upon brief synaptic input, these neuroendocrine cells undergo a synchronous burst of action potentials, known as the afterdischarge, culminating in the secretion of egg-laying hormone into the bloodstream. Near the start of the afterdischarge, cAMP levels are elevated. While it is well-established that cAMP inhibits K+ channels, thereby increasing excitability, nothing is known of the effects of this second messenger on electrical transmission in bag cell neurons. Here, we used pairs of cultured bag cell neurons and whole-cell recording to investigate the impact of cAMP on electrical coupling. Presynaptic action potentials consistently evoked postsynaptic electrotonic potentials, while presynaptic hyperpolarization was transferred accordingly to the postsynaptic cell. Delivery of a membrane-permeable cAMP analogue increased the electrotonic potential by ~25%, which was accompanied by a similar change in coupling coefficient. In addition, input resistance was also augmented by ~100%. These outcomes suggest cAMP may enhance electrical transmission, and as a consequence, influence synchronous firing during the afterdischarge.

1-B-15: Desensitization of cholinergic receptors maintain afterdischarges in Aplysia neuroendocrine cells

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[1]Queen's University

Prolonged change in neuronal output following transient stimulation is a ubiquitous yet incompletely understood phenomenon. The snail, Aplysia, engages in reproductive behavior when a brief, cholinergic input to its neuroendocrine bag cell neurons evokes a prolonged afterdischarge and the secretion of egg-laying hormone. The cholinergic input acts on

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ionotropic receptors, and the resulting depolarization is thought to orchestrate continuous firing by recruiting persistent Ca2+ current. Here, we used whole-cell recordings from cultured bag cell neurons to examine the involvement of Ca2+ current and cholinergic receptor desensitization in the control of long term change to activity. Delivering voltage-ramps designed to mimic the acetylcholine-induced depolarization caused prolonged Ca2+ influx that was sensitive to Ca2+ channel blockers (Ni2+, Co2+, Zn2+). In addition, when acetylcholine, but not the nicotinic agonist, tetramethylammonium, was repeatedly pressure-ejected onto a voltage-clamped neuron, subsequent currents were ~40% smaller than the first. This occurred at intervals of 10-120 min between first and second applications, although desensitization was nearly complete at intervals of ≤3 min. Moreover, desensitization was not observed ~24 hr between exposures to acetylcholine, which is consistent with the ~18-hr refractory period presented by the afterdischarge in vivo. These results suggest that fine channel-state dependence determines neuronal electrochemical responsiveness, which may be imperative for the complex sequence of molecular events required for behavior.

1-B-16: A novel role for the Neogenin receptor in cortical function

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Normal function of neuronal networks relies on a balance between excitation (E) and inhibition (I), and disruption of this balance is proposed to underlie certain neurodevelopmental disorders. A recent study linking the transmembrane receptor Neogenin (Neo1) with autism spectrum disorders (ASD) in humans, combined with in vitro findings suggesting Neo1 modulates cortical neuron development, motivated us to investigate a potential role for Neo1 in regulating E/I balance in the cortex. We show that Neo1 is expressed in both excitatory and inhibitory cortical neuron populations and can be detected at excitatory and inhibitory synapses. Specific ablation of Neo1 expression in the mouse nervous system revealed that Neo1 is dispensable for the generation of excitatory and inhibitory neurons that populate the somatosensory cortex. In contrast, loss of Neo1 leads to increased inhibitory synaptic transmission and altered E/I balance in layer 2/3 of the somatosensory cortex. We explore potential molecular mechanisms through which Neo1 may modulate synaptic transmission and influence homeostasis in cortical neurons of the somatosensory cortex.

1-B-17: Striatal neurons regulate neural stem cell fates through secreted molecules

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The adult subventricular zone (SVZ) niche contains neural stems cells (NSCs) that maintain and regenerate the brain by producing neurons, astrocytes and oligodendrocytes throughout life. Directly adjacent to the SVZ is the striatum; a region that is important in movement regulation and is rich in GABAergic neurons. While striatal neurons are known to project into NSC-rich SVZ niche, the significance of striatal neuron - SVZ NSC cell-cell communication is not currently known. I hypothesize postnatal SVZ NSCs fates are regulated by striatal neurons. To address this question, I cultured postnatal primary murine SVZ NSCs in control media or media conditioned by primary striatal neurons. My data show striatal neurons

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secrete soluble molecules that instruct SVZ NSCs to differentiate into oligodendrocytes and neurons without affecting astrocyte formation or NPC proliferation. To further investigate the pro-oligodendrogenic influence of the striatal neuron secretome, we cultured SVZ oligodendrocyte precursor cells (OPCs) in media conditioned by striatal neurons. Our data demonstrate striatal neuron conditioned media causes an increase in OPC differentiation into oligodendrocytes. Using RNA-seq datasets of purified striatal neurons and SVZ NSCs, I then computationally predicted over 80 striatal neuron ligands that have the potential to regulate SVZ NSC biology. In summary, my results suggest striatal GABAergic neurons may play an important role in regulating SVZ NSCs. Future work will determine which striatal neuron ligands are responsible for the observed pro-neurogenic and -oligodendrogenic effects and identify the in vivo significance of these molecules in the SVZ niche.

1-B-18: Probing dendritic spine cytoskeleton dynamics with the pannexin 1 blocker probenecid

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Dendritic spines are postsynaptic structures that arise from dynamic protrusions. Spine formation is a critical facet of synapse formation and aberrant spine properties are a hallmark of many neurodevelopmental disorders. Our lab previously found that expression levels of channel-forming protein pannexin 1 (PANX1) decrease during the period of spine formation. Panx1 knockout (KO) increased spine density and PANX1 overexpression reduced their stability and density. Unpublished results from our lab reveal that probenecid, a PANX1 blocker and Health Canada- and FDA-approved drug, recapitulated the effects of Panx1 KO. Early postnatal acute and chronic administration of probenecid led to increased somatosensory layer 5 cortical neuron spine density in situ. The current study aims to investigate the mechanism underlying probenecid regulation of dendritic spines, and capitalizes on our previous finding that probenecid interferes with a physical interaction between PANX1 and microtubule-stabilizing protein. To gain insight into spine cytoskeleton dynamics during development, we treated neurons with probenecid and imaged microtubule and actin dynamics within spines using microtubule plus-end binding probe EB3-GFP and actin-binding protein Lifeact. In parallel, we monitored spine dynamics using membrane-bound mCherry to understand the relationship between microtubule and actin dynamics and overall spine movement. This work will advance our understanding of dendritic spine development with implications for understanding the cellular mechanisms underlying neurodevelopmental diseases.

1-B-19: Age-dependent increase of sag current in human pyramidal neurons dampens noise in cortical sensory processing

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Aging involves a variety of neurobiological changes, although their effect on brain function remains poorly understood due to limited experimental capabilities in humans. The growing

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availability of human neuronal and circuit data provides an opportunity to uncover age-dependent changes at finer scales of brain networks and constrain detailed computational models to study the related effects on brain function. Here we analyzed sag voltage in human layer 5 pyramidal neurons and found a significant increase in old vs. young. We then generated models of young and old pyramidal neurons capturing the experimental changes and simulated them in layer 5 microcircuits. We found that old microcircuits had lower baseline and response rates than young microcircuits, but an overall enhanced signal-to-noise ratio due to a larger effect on baseline firing rates. Accordingly, the reduced noise in microcircuit output with age enabled a higher accuracy of stimulus discrimination. These age effects were principally due to changes in dendritic conductance mechanisms underlying the measured changes in sag properties. Our results report an age-dependent increase in human pyramidal neuron sag current, which reduced cortical firing noise and improved sensory processing in simulated microcircuits, and thus could serve as a target for modulation to ameliorate age-associated cognitive decline.

1-B-20: Microglial depletion increases non-rapid eye movement sleep duration in female mice

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Recent studies revealed that microglial functions differ along the sleep-wake cycle, albeit their contribution to sleep regulation remains elusive. Given a higher prevalence of sleep disorders in women, we aimed to determine the role of microglia in regulating the sleep-wake cycle in adult C57BL/6J female mice. We investigated the effect of microglial depletion with the colony stimulating factor-1 receptor antagonists, PLX3397 or PLX5622, on the sleep/wake cycle. Microglial depletion was confirmed by immunofluorescence against IBA1 and TMEM119. We compared the spontaneous sleep/wake cycle before and after microglial depletion as well as after microglial repopulation of the brain. Microglia-depleted mice had increased time spent in the non-rapid eye movement (NREM) sleep that was rescued by microglial repopulation. Mice depleted in microglia also exhibited an increased number of NREM sleep episodes, partially restored by microglial repopulation. Furthermore, in the light phase, microglia expressed higher levels of the fractalkine receptor (Cx3cr1) in the motor cortex, but lower levels in the thalamus, suggesting that microglia adapt their Cx3cr1 expression in response to the light/dark phase in a region-specific manner. Excitatory synaptic transmission was furthermore increased in the light phase in the motor cortex, but was not affected by microglial depletion. Altogether, our findings indicate for the first time that microglia play an important role in the regulation of sleep and strengthen their potential involvement in the development or progression of sleep disorders.

1-B-21: The effects of the NMDAR co-agonist D-serine on the structure and function of the optic tectum

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The N-methyl-D-aspartate type glutamate receptor (NMDAR) is a molecular coincidence detector thought to convert patterned neuronal activity into cues for structural and functional topographic refinement. How NMDARs orchestrate activity-dependent circuit plasticity has mostly been characterized through loss-of-function manipulations, but these can disrupt normal development or have non-specific effects. Our lab demonstrated that signal enhancement of NMDAR by D-serine, an endogenous co-agonist of the NMDAR, promotes glutamatergic synapse maturation, and stabilizes axonal structural and functional inputs in the developing visual system of the Xenopus tadpole. Here, we further investigate how NMDAR signal enhancement contributes to the refinement of this retinotectal circuit by studying the effects of D-serine exposure on tectal morphology and function. Using in vivo two-photon imaging, we report that postsynaptic dendritic arbors from animals reared in D-serine showed increased compaction, reduced dynamics, and higher synaptic density, specifically for recently differentiating neurons rather than globally in the tectum. To examine functional changes to the circuit, we used calcium imaging to extract the retinotopic map, and showed a sharpening of tectal cell receptive fields in animals raised in D-serine. Together, these suggest that the availability of the D-serine at glutamatergic synapses modulates activity-dependent NMDAR-mediated refinement of the developing retinotectal circuit. Funding: CIHR Foundation grant to ESR, NSERC CGS-M and IPN Awards to ZC and VL.

1-B-22: Suppressing CSPGs receptors enhances spinal specific neuronal replacement by human directly reprogrammed neural precursor cells and improves functional recovery after spinal cord injury

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Spinal cord injury (SCI) results in neurodegeneration and damage to the spinal neural circuitry. To date, effective neuronal replacement and functional restoration of spinal circuit remain challenging. Transplantation of neural precursor cells (NPCs) offers a promising approach for neuronal replacement in SCI. However, our studies indicate limited neurogenesis by transplanted NPCs in the hostile milieu of SCI. We identified that injury-induced upregulation of chondroitin sulfate proteoglycans (CSPGs) hinders survival and integration of engrafted NPCs after SCI by signaling through two main receptors, LAR and PTP-σ. Here, we have evaluated the therapeutic potential of co-blocking LAR and PTP-σ by ILP and ISP peptides, respectively, in conjunction with transplantation of human directly reprogrammed NPCs (drNPCs) with the capacity to generate spinal neurons. Our in vitro studies confirmed ILP/ISP co-treatment restores the inhibitory effects of CSPGs on drNPCs and promotes their neuronal differentiation, maturation, and synaptogenesis. In rat SCI, systemic delivery of ILP/ISP significantly promoted long-term survival and biodistribution of human drNPCs, enhanced their neuronal differentiation and complexity, and functional recovery after SCI. Our transcriptomic analysis identified that CSPGs impede neuronal differentiation by inactivating the Wnt/β-catenin pathway, which was verified in our in vitro studies. Altogether, we have developed a new targeted, translationally feasible strategy with the potential to optimize neuronal replacement and functional recovery after SCI.

1-B-23: The role of endoplasmic reticulum stress in cannabinoid-mediated neuroprotection

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The aggregation of misfolded proteins in the endoplasmic reticulum (ER) is a pathological trait shared by neurodegenerative disorders. This aggregation leads to the persistent activation of the unfolded protein response (UPR), and ultimately apoptosis. Cannabinoids, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), have been reported to be neuroprotective in in vitro and in vivo models of neurodegeneration through their antioxidant and anti-inflammatory properties. However, little is known about the role of these cannabinoids in the context of ER stress. Using a cellular model of ER stress, we investigated the neuroprotective effects of THC and CBD and the genes which mediate cell survival. Mouse striatal neurons were preconditioned with either 2.5 μM THC, 1 μM CBD, or a combination of both, followed by an ER stress inducer, thapsigargin. Cell viability increased significantly with THC and CBD alone but was not significantly altered when combined before ER stress induction. Gene and protein expression was measured to determine the effect of cannabinoid preconditioning on pro-survival UPR proteins. A significant increase in Bip, MANF, and Bcl-2 suggests that exposure to cannabinoids before ER stress induction may shift the UPR to a more adaptive response. These data suggest that cannabinoid monotherapy prepares the cell for future insults to the ER. Understanding the role of ER stress in the neuroprotective properties of THC and CBD provides insight into the therapeutic potential of cannabinoids and the role of ER dysfunction in various neurodegenerative disorders.

1-B-24: Huntingtin reduction unmasks an active form of NMDAR-dependent synapse loss

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[1]Memorial University of Newfoundland

Huntington disease (HD) is monogenic and caused by a CAG repeat expansion in the IT15 gene, which results in the production of a mutant huntingtin protein (mHTT). In addition to the production of this pathogenic variant, HD patients generate half the amount of wild type huntingtin (wtHTT). Although wtHTT has a well-established role in neurodevelopment, as its knockout is embryonic lethal, its exact role in the adult brain is not well understood. Recent literature suggests a major role for wtHTT in synaptic function in adult neurons, specifically loss of wtHTT impairs presynaptic vesicle release as well as postsynaptic receptor localization. We hypothesized that these synaptic impairments may lead to defects in NMDAR-dependent long term potentiation (LTP)-induced changes in hippocampal wtHTT-lowered neurons. Chemical LTP (cLTP) was induced using glycine in primary hippocampal cultured neurons and wtHTT levels were lowered by siRNA application. Both presynaptic synaptophysin (SYP) and postsynaptic PSD-95 were labelled by immunofluorescence. Using super-resolution microscopy, we quantified the density of SYP and PSD-95 puncta from individual dendrites at the nanoscale level. cLTP induction revealed an activity-dependant decrease in SYP, but not PSD-95, density in wtHTT-lowered cells. These findings indicate a potential switch from synaptic potentiation to depression and subsequent loss of synapses during hippocampal NMDAR activation due to wtHTT lowering. Understanding these outcomes is essential as many HD genetic therapies in development further lower patient wtHTT levels.

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1-B-25: Electrophysiological properties of neurons in the primary auditory cortex of the Cntnap2 KO rat model for autism

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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 at a cellular level in the auditory cortex of a Cntnap2-/- rat model, hypothesizing that Cntnap2 is essential for maintaining intrinsic neuronal properties and excitability in the auditory cortex. Whole-cell patch clamp recordings were performed in brain slices from juvenile (P8-12 and P18-21) and adult (P70-90) wildtype (Cntnap2+/+) and knockout (Cntnap2-/-) rats. Intrinsic membrane properties, spontaneous EPSCs and firing patterns of cortical pyramidal cells were assessed. Action potentials were significantly larger in Cntnap2-/- rats at P8-12 and P18-21, and Cntnap2-/- rats at both P8-12 and P18-21 exhibited smaller half-widths compared to wildtypes. Compared to wildtypes, Cntnap2-/- rats exhibited larger sEPSCs at P8-12, but they were smaller at P18-21 and P70-90. The Cntnap2-/- rats also had higher sEPSC frequencies at P70-90, but there were no differences at the younger ages. These results indicate that intrinsic cell properties and activity are altered in Cntnap2-/- rats, but these differences are not consistent across the ages. These experiments will provide novel insights into how Cntnap2 impacts auditory processing at a cellular level, and shed light on the neural mechanisms underlying altered auditory processing seen in Cntnap2-/- rats.

1-B-26: Differential subcellular distribution of co-transmitted cholinergic and GABAergic synaptic inputs onto substantia nigra dopaminergic neurons

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The present study investigated the subcellular localization and physiological nature of acetylcholine (ACh)/GABA co-transmission from cholinergic axons synapsing onto medial substantia nigra (SN) dopaminergic (DA) neurons. Using optogenetic stimulation of cholinergic terminals, we discovered three types of monosynaptic cholinergic inputs spatially segregated onto medial SN DA neurons: co-transmitted ACh/GABA, GABA only, and ACh only. Input mapping revealed a predominant GABA conductance along lateral dendrites and soma-centered ACh/GABA co-transmission. Furthermore, the lateralized GABA conductance was more sustained across repeated stimulations compared to the proximal GABA conductance, which greatly depressed with repeated stimulation. Optical stimulation of lateral GABA inputs was also more effective in suppressing action potential firing. Soma-localized ACh/GABA co-transmission showed that the initially dominant GABA component depressed while the ACh-mediated nicotinic responses were maintained. We investigated whether this plastic change in competing inhibitory/excitatory inputs leads to altered neuronal excitability. We found that a depolarizing current or glutamate preceded by co-transmitted ACh/GABA was more effective in eliciting an action potential as compared to current, glutamate, or ACh/GABA alone. However, this enhanced excitability was abolished with nicotinic receptor inhibitors, T- and L-type calcium channels. This work has advanced

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our understanding of how spatiotemporal integration of synaptic inputs influences SN DA neuronal excitability.

1-B-27: The ATRX chromatin remodelling is required in astrocytes for long-term recognition memory

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Astrocytes are glial cells of the central nervous system that regulate synapse formation, maturation and elimination. Defective astrocytes can alter synaptic transmission and contribute to disease, as in monogenic neurodevelopmental disorders Rett and Fragile X syndromes. Alpha Thalassemia X-linked intellectual disability (ATR-X syndrome) is a neurodevelopmental disorder caused by mutations in the ATRX gene. We hypothesize that ATRX controls chromatin structure and the expression of astrocytic genes required for normal cognition. Here, we generated mice with tamoxifen-inducible Atrx inactivation in astrocytes (Atrxf/y;GlastCreER or ATRX aiKO,). Tamoxifen was injected from postnatal day 10 to 12 to induce Atrx deletion in astrocytes prior to maturation. Immunofluorescence staining of ATRX and cell type specific markers show that ATRX is absent in approximately 50 % of the astrocytes in the cortex and hippocampus of ATRX aiKO mice. Behavioural tests to assess different types of memory, novel object recognition and Morris water maze, show that ATRX aiKO mice exhibit long-term recognition and spatial memory deficits compared to controls. Ex vivo electrophysiology measurements, dendritic branching and spine morphology of CA1 neurons revealed reduction in synaptic function of hippocampal CA1 neurons but normal morphology. Astrocyte nuclei were purified using fluorescence activated nuclei sorting (FANS) and used for RNA-sequencing. Analysis of the transcriptome revealed altered expression of genes associated with cytoskeleton and synapse organization. Collectively, these findings demonstrate that astrocytic ATRX regulates gene expression and promote normal synaptic transmission in neighbouring hippocampal neurons, thus contributing to long-term memory processes.

1-B-28: Exploring the location dependence of NMDA receptors in synaptic plasticity

Sabine Rannio[1], Aurore Thomazeau[1], Gemma Moffat[1], Claire Ko[1], Per Jesper Sjöström[1]

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In the classical view, the postsynaptic NMDAR (postNMDAR) acts as a coincidence detector and causes synaptic strengthening when connected neurons are simultaneously active, a concept known as Hebbian plasticity. However, NMDARs may also be expressed presynaptically (preNMDARs), where they control both short- and long-term plasticity. We recently showed that preNMDARs regulate evoked and spontaneous release by two independent signalling cascades. Here, we explore the roles of pre- and postNMDARs in synaptic plasticity. To achieve sparse genetic deletion of NMDARs, we created the triple transgenic mouse model Emx1Cre/+;Ai9tdTom/+;NR1flox/flox. Using MNI-NMDA uncaging in acute slices (postnatal days 11 to 18), we verified that postNMDARs were deleted in pyramidal cells (PCs) (0.020 ± 0.5 pA, n=31 vs. control -48 ± 6 pA, n=19; $p<0.001$). We previously showed that AP5 or Ro25-6981 reduce spontaneous release rates in PCs by blocking preNMDARs. However, these drugs did not affect mEPSC frequency in NMDAR deletion mice (AP5 85% ± 10%, n=10, vs. control 60% ± 20%, n=4, p=0.19; Ro 89% ± 15%,

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n=7, vs. control 66% ± 10%, n=8; p=0.53), consistent with successful preNMDAR deletion. We also observed that NMDAR deletion caused distinct changes in PC morphology, which we are quantifying by 3D reconstruction and spine counts. With this NMDAR deletion mouse model established, we will next use paired recordings to show how pre- and postNMDARs differentially influence short and long-term synaptic plasticity.

1-B-29: Spike-timing-dependent plasticity at neocortical vip interneuron outputs

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Many anti-epileptic drugs control activity via GABAergic neurotransmission mediated by inhibitory neurons (INs). Of all IN types, vasoactive intestinal peptide-expressing (Vip) INs are particular poorly described, e.g., little is known about their plasticity. Yet, Vip INs increase seizure susceptibility and duration by inhibiting nearby INs. As Vip INs provide a promising seizure control point, we set out to characterize the plasticity of Vip INs in the mouse cortex to determine how it can be harnessed for seizure control. We bred transgenic mice that express Channelrhodopsin-2 (ChR2) in Vip INs by crossing Vip-Cre and ChR2 reporter mice (Ai32-flox). In acute slices of Vip-ChR2 mice, we targeted Martinotti cells (MCs) and basket cells (BCs) for whole-cell recording and activated presynaptic Vip INs with a 445-nm laser to explore how plasticity of Vip IN outputs depend on spike rate and timing. We found that specific MC disinhibition was possible by inducing spike-timing-dependent long-term depression (tLTD) at 50 Hz firing rate and pre-before-postsynaptic timing difference of Δt = +10 ms (77% ± 7%, n = 6, $p < 0.05$). In contrast, we found no plasticity at other tested timings and frequencies (50 Hz and Δt = -10 ms; 50 Hz and Δt = +25 ms: 20 Hz and Δt = ±25 ms; pooled: 98% ± 6%, n = 20, $p = 0.79$). We found that LTD was induced at Vip-BC connections irrespective of temporal order (50 Hz and Δt = ±10 ms pooled: 79% ± 10%, $p < 0.05$). Next, we aim to assess the impact of Vip IN plasticity on ictal-like activity in acute slices with the 4-AP in-vitro model of epilepsy.

1-B-30: The role of ferroptosis in iron toxicity following spinal cord injury

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Ferroptosis is a newly identified-form of programmed cell death, which is triggered by excess intracellular iron and deficient antioxidant defense, leading to iron-dependent lipid peroxidation. One molecular pathway of ferroprosis occurs through NCOA4, a shuttle protein that transports cytosolic ferritin to autophagosomes for degradation, resulting in the release of iron from ferritin, which subsequently stimulates lipid peroxidation. In spinal cord injury (SCI), one of the immediate consequences of trauma is rupture of blood vessels. Elevated level of iron due to infiltration of red blood cells to the site of injury increases the possibility that ferroptosis might be involved in secondary damage associated with SCI. However, the role of ferroptosis in SCI remains unclear. We have previously shown that iron accumulation in CD11b+ macrophages is seen rapidly after SCI. We now show increased expression of NCOA4 in the first two weeks after contusion injury in mice. NCOA4 was expressed in microglia/macrophages at the site of SCI lesions and was associated with reduced ferritin. We found that some NCOA4+ cells showed signs of cell death. In addition, protein levels of

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the antioxidant enzyme glutathione peroxidase 4 (GPX4) remains unchanged after SCI, indicating it may be insufficient to handle increased lipid peroxidation that causes ferroptosis. Treatment with a ferroptosis inhibitor (UAMC-3203), showed a small but significant improvement in locomotor recovery indicated by the BMS score and subscore. These findings indicate that NCOA4 may contribute to ferroptosis mediated iron toxicity in SCI.

1-B-31: Developmental profile of visual cortex astrocytes

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By sensing neuronal signalling, astrocytes release gliotransmitters triggered by intracellular calcium (Ca2) transients. This is involved in the regulation of synaptic plasticity. To improve our understanding of layer-5 (L5) neocortical astrocytes in mouse visual cortex, we investigate their developmental profile between postnatal days (P) 9 - 22. Using 2-photon microscopy in acute slices, astrocytes were targeted for patching with Sulforhodamine 101. L5 astrocyte Vm was -82 ± 0.4 mV and Rinput was 34 ± 2 MΩ (n = 127). Over the ages P9-22, Vm increased (Pearson's r = 0.271, $p < 0.01$) and Rinput decreased (r = -0.189, $p < 0.05$). Within L5, astrocytes exhibited diverse electrophysiological responses due to voltage steps. Hierarchical clustering indicated two or possibly more response classes, with one class showing a steady, time-invariant conductance and the others a slowly activating component. This slowly activating conductance vanished with age (Spearman's rho = -0.44, $p < 0.05$, n = 22). We next investigated the development of spontaneous Ca2 transients, visualized with Fluo-5F (200 µM) or AAV-GCaMP6f. We found that Ca2 transients in different compartments of an astrocyte decorrelated with age (r = -0.57, $p < 0.01$, n = 20), which might be explained by development and maturation of processes. Gap-junction coupling and morphological reconstructions over development were also investigated using Alexa 488 loading. This study provides a foundation for our future work to understand how astrocytes in visual cortex L5 regulate neocortical plasticity at excitatory synapses.

1-B-32: Schizophrenia-associated LRRTM1 regulates cognitive behavior through controlling synaptic function in the mediodorsal thalamus

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

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functionally disengages the MD from the PFC and may account for cognitive, social, and sensorimotor gating deficits, reminiscent of schizophrenia.

1-B-33: Clustering dendritic spines morphological properties after odour stimulation and learning

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The ability to store new information and to adapt to new environments is a crucial neurobiological 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. We propose a computational pipeline to reconstruct and analyse dendritic spines from confocal microscopy images into a 3D mesh model. First, we acquired confocal, high resolution images of distal dendritic segments from adult born neurons in the olfactory bulb (OB) after odour learning using a simple and complex go/no-go odour discrimination paradigm and after sensory deprivation. The reconstruction of dendritic spines images was performed in 4 steps i) correction of image stacks via deconvolution and diffraction correction, ii) 3D segmentation, iii) reconstruction into a 3D mesh and iv) automatic extraction of spines and measure of features. Recent papers suggest that clusterization instead of classification is more appropriate to describe spines because spine morphologies are continuous. Thus, instead of manually categorizing spines, we assessed several spine features such as the length, surface, open angle, etc., and analysed these features with machine learning. We performed dimension reduction and we then identified some clusters associated with spines' morphological features. We report a significant increase in surface and in open angle as well as a decrease in Hull ratio in the mice of odour learning group as compared to control animals.

1-B-34: Functional impact of aging on mouse prefrontal cholinergic synapses: an optophysiological investigation

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Cholinergic modulation of the prefrontal cortex is essential for higher brain function. Changes in cholinergic markers have been reported in brains of healthy aged adults and those with dementia. Disturbances in fibers, enzymes, and receptors are hypothesized to underlie age-related cognitive dysfunctions; however, their integrated impact on cortical cholinergic signalling is not well understood. Here, we use optogenetics and whole cell electrophysiology to investigate functional properties of cholinergic synapses across a broad age range in adulthood. We use prefrontal brain slices from transgenic mice expressing excitatory opsin in cholinergic basal forebrain neurons whose axons project to the cortex and release acetylcholine when stimulated with light. We demonstrate that pyramidal neurons in the aged brain show changes in the properties of their responses to optogenetically-released acetylcholine. Direct excitation of cholinergic receptors on pyramidal neurons declines with age. Ongoing experiments are probing the impact of aging on specific contributions of presynaptic and postsynaptic components of the synapse. In addition, we are investigating age-dependence in the sensitivity of cholinergic signalling to allosteric modulation and other

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treatment interventions. Understanding the impact of aging on synaptic mechanisms of cholinergic transmission is important to understand cognitive resilience and gain a better appreciation for effective targets to treat cognitive impairment.

1-B-35: Sex-specific retinal anomalies induced by chronic social stress in mice

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Major depressive disorder (MDD) is one of the most common consequences of chronic stress. Still, there is currently no reliable biomarker to detect individuals at risk to develop the disease. Recently, the retina emerged as an effective way to investigate psychiatric disorders using the electroretinogram (ERG). In this study, rod ERGs were performed in male and female C57BL/6 mice before and after chronic social defeat stress (CSDS). Mice were then divided as susceptible or resilient to stress. Our results suggest that CSDS reduces the amplitude of both oscillatory potentials and a-waves in the rods of resilient but not susceptible males. In females, rods ERGs only revealed age-related changes. Finally, our analysis suggests that baseline ERG can predict with an efficacy up to 71.5% the expression of susceptibility and resilience before stress exposition in males and females. Overall, our findings suggest that retinal activity is a valid biomarker of stress response that could potentially serve as a tool to predict whether males and females will become susceptible or resilient when facing CSDS.

1-B-36: Exploration of inhibitory system maturation in neuronal cultures with multimodal imaging techniques: toward a methodology to identify cellular biomarkers of schizophrenia

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Schizophrenia (SZ) is a psychiatric disease affecting about 1% of the population. Increasing evidence shows that cortical alterations of the maturation and function of inhibitory systems inducing perturbations in the excitatory/inhibitory (E/I) balance are likely to be involved in the pathogenesis of SZ. We propose that a delay of the GABA switch from excitatory to inhibitory during neurodevelopment could explain the perturbations of the E/I balance and represent a cellular phenotype of SZ. To assess this assumption, we aim to use a multimodal imaging approach including Digital Holographic Microscopy (DHM) to explore the neuronal functional maturation in in vitro cellular models. During early neurodevelopmental stages, GABA-mediated depolarization induces calcium (Ca2+) influx through voltage-gated Ca2+-channels. As a first step, Ca2+ responses to GABA stimulation have then been monitored at different ages in primary cultures of rat cortical neurons. The percentage of neurons responding to GABA decreased overtime suggesting a loss of GABA depolarizing action during neuronal maturation. We are now evaluating the relationship between Ca2+ responses and the label-free DHM measurements of transmembrane water fluxes related to GABAA receptors and (N)KCC cotransporters activities. We aim to use this methodology to

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explore the maturation of iPSC-derived cortical neurons obtained from patients with SZ, high-risk offspring and controls. Such non-invasive detections of functional alterations during the neurodifferentiation process could help to identify risk biomarkers of SZ.

1-B-37: Phosphorylation-dependent control of Activity-regulated cytoskeleton-associated protein (Arc) protein by Tnik

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The remarkable capacity of neurons to reorganize their structure, function, and connections in an activity-dependent manner is supported by an extensive network of molecules and effectors. Among those, the 'hub' protein Activity-regulated cytoskeleton-associated protein (Arc, also known as Arg3.1) can be considered one of the central, as well as most versatile, players. Notably, Arc has been shown to maintain direct interactions with key synaptic factors like PSD95, TARPγ2, and CaMKII, as well as participate in many aspects of neuroplasticity such as trafficking of AMPARs and modeling of dendritic spines. How a single protein like Arc can do all this remains difficult to explain, but a complete answer to that question will certainly include a mix of protein post-translational modifications acting to confer molecular and functional specificity. Recently, sequence analysis of Arc protein led us to recognize two candidate phosphorylation sites specific to TRAF2 and NCK-interacting protein kinase (TNIK)--a member of the Germinal Center Kinases (GCK) subfamily that is considered a possible risk factor to different psychiatric disorders, including schizophrenia and bipolar disorder. Here, we present extensive biochemical, proteomics, and electron microscopy evidence supporting the influence of TNIK on Arc's subcellular distribution and oligomerization. Together, our findings position Arc as a substrate of TNIK and offer exciting new scenarios implicating these two factors in the context of the pathophysiology and potential treatment of neuropsychiatric disorders.

1-B-38: Atypical NMDA receptors limit synaptic plasticity in the adult ventral hippocampus

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The dorsal and ventral hippocampus (DH and VH) are dramatically different structures. The DH is involved in cognition and undergoes robust synaptic plasticity while the VH functions in emotional processing and naturally exhibits poor plasticity. N-methyl-D-aspartate receptors (NMDARs) assemble as functionally diverse heterotetramers with essential roles in synaptic plasticity. Incorporation of the GluN3A subunit into NMDARs alters conventional NMDAR properties, delays synapse maturity, and opposes synaptic plasticity. Consistent with recent reports, we show that GluN3A remains elevated, mainly in extrasynaptic locations, in the adult VH but not the DH. Despite GluN3A persistence, VH spines matched the maturity level observed for the DH. As presynaptic and postsynaptic GluN3A-NMDARs can facilitate glutamate release and limit Ca2+ permeability, we performed real-time glutamate and calcium imaging to further understand the consequences of GluN3A persistence in the adult

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VH. Compared to the DH, the VH accumulated more glutamate during afferent stimulation yet exhibited less NMDAR-mediated Ca2+ influx. We then hypothesized that prolonged GluN3A expression limits synaptic plasticity in the VH. Indeed, in wildtype mice, long-term potentiation (LTP) was significantly lower in the VH compared to the DH. In contrast, GluN3A knockout (KO) mice exhibited strong VH LTP that now exceeded the magnitude of LTP in the DH. In sum, our data show that GluN3A persistence limits VH plasticity in adulthood, perhaps serving a protective role to prevent overexcitation of anxiety and fear circuitry.

1-B-39: Opioid peptides exert direct and indirect effects on striatal nitrergic low threshold spiking (LTS) interneurons

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Dynorphin A and enkephalin are opiate peptides that are found in the direct and indirect pathway Medium spiny neurons respectively. Although the opioid system in the striatum plays a crucial role in reward processing, the opioidergic modulation of striatal interneurons is still poorly understood. Furthermore, the nitrergic low threshold spikes (LTS) and the cholinergic interneurons are striatal neurons that modulate the final striatal output. The nitrergic (LTS) interneurons secrete many neurotransmitters (i.e. somatostatin, GABA, NO, and NPY). While the cholinergic interneurons are the main source of acetylcholine in the striatum. In this study, we aimed at studying of the effect of δ and κ opiate receptor agonists on the nitrergic and the cholinergic interneurons. We used transgenic mice in which the NPY is marked with a green fluorescent protein (GFP). Moreover, we carried out whole-cell and cell-attached recordings from mice brain slices maintained in vitro. Our data report that δ receptor agonist (DPDPE; 1 μM) and κ receptor agonist (U-50488 hydrochloride; 10 μM) reversibly inhibited the nitrergic and the cholinergic interneurons. This inhibitory effect on the nitrergic interneurons persisted in the presence of nicotinic and muscarinic receptor antagonists, and tetrodotoxin (TTX) (1μM). Finally, we found that DPDPE but not U-50488 inhibited the GABAergic transmission on the LTSIs. Taken together our results demonstrate that δ & κ opioid peptides exert direct and indirect effects on the nitrergic LTSIs. These results help us to understand more about striatal microcirculatory and how opioid peptides can modulate striatal output.

C - Disorders of the Nervous System

1-C-40: Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury

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Spinal cord injury (SCI) induces hemodynamic instability that threatens survival, impairs neurological recovery, increases cardiovascular disease risk, and reduces quality of life. Hemodynamic instability in this context is due to the interruption of supraspinal efferent commands to sympathetic circuits located in the spinal cord, which prevents the natural baroreflex from controlling these circuits to adjust peripheral vascular resistance. We

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previously showed that epidural electrical stimulation (EES) of the spinal cord can compensate for interrupted supraspinal commands to motor circuits below injury, which restored walking after paralysis. Here, we leveraged these concepts to develop EES protocols that restored hemodynamic stability after SCI. We established a novel preclinical model that enabled us to dissect the topology and dynamics of the sympathetic circuits, and understand how EES can engage these circuits. We incorporated these spatial and temporal features into stimulation protocols to conceive a clinical-grade biomimetic hemodynamic regulator operating in closed-loop. This neuroprosthetic baroreflex controlled hemodynamics for extended periods of time in rodents, non-human primates, and humans, both after acute and chronic SCI. We will now conduct clinical trials to turn the neuroprosthetic baroreflex into a commonly available therapy for people with SCI.

1-C-41: Decreasing mitochondrial fragmentation is protective in C. elegans models of Huntington's disease

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Huntington's disease (HD) is an adult onset neurodegenerative disease caused by a trinucleotide CAG repeat expansion in the HTT gene. While the pathogenesis of HD is incompletely understood, mitochondrial dysfunction is thought to be a key contributor. In this work, we used C. elegans models to elucidate the role of mitochondrial dynamics in HD. We found that expression of a disease-length polyglutamine tract in body wall muscle, either with or without exon 1 of mutant huntingtin, results in the disruption of mitochondrial networks. While the mitochondrial network in young worms form elongated tubular networks as in wild-type worms, mitochondrial fragmentation occurs as expanded polyglutamine protein forms aggregates. To correct the deficit in mitochondrial morphology, we reduced the levels of DRP-1, the GTPase responsible for mitochondrial fission. Surprisingly, we found that disrupting drp-1 can have detrimental effects, which are dependent on how much the expression is decreased. To avoid potential negative side effects of disrupting drp-1, we examined whether decreasing mitochondrial fragmentation by targeting other genes could be beneficial. Through this approach, we identified multiple genetic targets that rescue movement deficits in worm models of HD. Three of these genetic targets, pgp-3, F25B5.6 and alh-12, ameliorated movement deficits in the HD worm model and restored mitochondrial morphology to wild-type. This work demonstrates that disrupting the mitochondrial fission gene drp-1 can be detrimental in animal models of HD, but that decreasing mitochondrial fragmentation by targeting other genes can be protective. Overall, this study identifies novel therapeutic targets for HD aimed at improving mitochondrial health.

1-C-42: The 5alpha-reductase inhibitor finasteride reduces opioid self-administration in animal models of opioid use disorder

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Opioid use disorder (OUD) has become a leading cause of death in the US, yet current therapeutic strategies remain highly inadequate. To identify novel potential treatments for OUD, we screened a targeted selection of over 100 drugs, using a recently developed opioid self-administration assay in zebrafish. This paradigm showed that finasteride, a steroidogenesis inhibitor approved for the treatment of benign prostatic hyperplasia and androgenetic alopecia, reduced self-administration of multiple opioids without affecting locomotion or feeding behavior. These findings were confirmed in rats; furthermore, finasteride did not interfere with the antinociceptive effect of opioids in rat models of neuropathic pain. Steroidomic analyses of the brains of fish treated with finasteride revealed a significant increase in dehydroepiandrosterone sulfate (DHEAS). Treatment with precursors of DHEAS reduced opioid self-administration in zebrafish, in a fashion akin to the effects of finasteride. Our results highlight the importance of steroidogenic pathways as a rich source of therapeutic targets for OUD and point to the potential of finasteride as a new option for this disorder.

1-C-43: Verapamil provides neuroprotection against hyperglycemic ischemic-reperfusion injury in primary neural cells: Involvement of thioredoxin interacting protein

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Admission hyperglycemia is a common concern in patients with ischemic stroke, predicting poor prognosis. Thioredoxin interacting protein (TXNIP) is intimately responsive to hyperglycemia, to drive oxidative damage partly through interacting with NOD-like receptor pyrin domain-containing-3 (NLRP3) inflammasome. In this in-vitro study, we demonstrate whether verapamil, an established TXNIP inhibitor, provides direct neuroprotection against hyperglycemic reperfusion. Oxygen glucose deprivation (OGD) was induced in primary cortical neural (PCN) cultures prepared from mice fetus brain. Cell survival experiment was performed at 24 h ischemic reperfusion (I/R) injury in cultures exposed to different verapamil concentrations in hyperglycemic medium. Immunoblotting and immunoprecipitation experiments were carried out to analyze the effect of glucose or verapamil on TXNIP expression or interaction with NLRP3 inflammasome. Based on our findings, increasing glucose concentration (2.5, 5 and 10 mM) directly correlates with TXNIP expression in PCN culture exposed to OGD, followed by reduced PCN survival at high glucose (HG) concentration (25 mM). Verapamil (100 Nm) produced significant protection against PCN cells injury at HG, along with reduced TXNIP expression. This was associated with moderate reduction in TXNIP interaction with NLRP3 inflammasome. These findings underline verapamil protection against HG-induced TXNIP upregulation as a potential therapy in hyperglycemic stroke.

1-C-44: Availability of neuregulin-1beta1 protects neurons in spinal cord injury and against glutamate toxicity through caspase dependent and independent mechanisms

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Spinal cord injury (SCI) causes sensorimotor and autonomic impairment that reflects loss of neurons at the epicenter and penumbra of the injury. Strategies aimed at enhancing neuronal protection are critical to attenuate neurodegeneration and improve neurological recovery after SCI. In rat SCI, we previously discovered that tissue levels of neuregulin-1beta 1 (Nrg-1β1) is acutely and persistently downregulated in the spinal cord and restoring its declined levels fosters oligodendrogenesis and promotes an anti-inflammatory, pro-regenerative response in glia and leukocytes, which culminates in improved functional recovery after SCI. While Nrg-1β1 is well-known for its critical roles in the development, maintenance and physiology of neurons and glia, its specific effects and mechanisms on neuronal injury remain unknown. In the present study, using a compressive/contusive rat SCI model and an in vitro model of glutamate toxicity in primary neurons, we demonstrate Nrg-1β1 provides early neuroprotection through attenuation of reactive oxygen species, lipid peroxidation, necrosis and apoptosis in acute and subacute stages of SCI. Mechanistically, availability of Nrg-1β1 following glutamate challenge protects neurons from caspase-dependent and independent cell death that is mediated by modulation of mitochondria associated apoptotic cascades and MAP kinase signaling pathways. Altogether, our work provides novel insights into the role and mechanisms of Nrg-1β1 in neuronal injury after SCI and introduces its potential as a neuroprotective target for this neurological condition.

1-C-45: Sex-specific cellular and molecular adaptations to chronic stress in the corticoaccumbal and corticotegmental pathways

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Background. Males and females respond differently to chronic stress. The medial prefrontal cortex (mPFC) is part of a complex circuit controlling stress responses and sends projections to other limbic structures including the nucleus accumbens (NAc) and ventral tegmental area (VTA). However, whether these pathways are differently involved in depressive-like behaviors following chronic stress in males and females is still unclear. Methods. We used chronic variable stress (CVS) to induce depressive-like behaviors in males and females and recorded electrophysiological measures in both projections. Chemogenetic was used to validate behavioral contribution of mPFC-NAc pathways to the expression of depressive-like behaviors. Finally, using RiboTag mice, we performed RNAseq to screen pathways specific transcriptional profiles. Results. CVS in females increases the frequency of sEPSCs in NAc and VTA projecting neurons. In males, CVS raises the frequency of sEPSCs only in VTA projecting mPFC neurons. These functional changes were accompanied by sex-specific morphological alterations. We showed that the chemogenetic activation of mPFC-NAc pathway increases stress susceptibility in both sexes while the inhibition of this pathway reverses stress-induced behavioral deficits in females only. Finally, our analysis revealed pathway-specific transcriptional alterations in males and females induced by CVS. Conclusion. Our results suggest that chronic stress impacts the corticoaccumbal and corticotegmental pathways differently through sex-specific morphofunctional alterations in mPFC neurons.

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1-C-46: Concomitant traumatic brain and spinal cord injury leads to working memory deficits without affecting sleep in rodents

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Traumatic brain and spinal cord injuries (TBI and SCI) can lead to long-term disabilities. Although the epidemiology, medical complications and prognosis of isolated TBI or SCI have been well described, there are limited data on sleep, emotional and cognitive behaviors for dual diagnosis. Our goal was to evaluate whether combined TBI and SCI modifies sleep phenotypes, emotional regulation and cognitive performance in a rat model. EEG activity was recorded in rats submitted to TBI-SCI (n=6), SCI alone (n=9) and in control (sham, n=8) rats before and at days 14 and 28 after injuries. The duration and quality of wakefulness and sleep was evaluated, notably using spectral analysis to compute delta activity during non-rapid eye movement (NREM) sleep. Emotional state was tested using the open-field and sucrose preference tests at the chronic phase (35 d.), together with working memory evaluation using the Y-maze test (42 d.). The duration and quality of wakefulness and sleep was not affected by SCI or TBI-SCI. Spectral analysis showed a tendency for TBI-SCI to increase NREM sleep delta activity after injury. Concomitant TBI-SCI did not affect anxiety-like and depressive-like behavior in comparison to the sham group. Working memory was significantly impaired after TBI-SCI but was preserved in sham and SCI groups. Only working memory was affected by TBI-SCI, defining it as a potential biomarker of this type of injury. Further experiments are needed to investigate the contribution of neuro-inflammation in the hippocampus to this phenotype.

1-C-47: Investigating the role of the immune cell response for successful spinal cord regeneration in the zebrafish model

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Spinal cord injury (SCI) is a life changing condition affecting individuals within Canada and worldwide with no effective treatment to date. A limitation in humans, like other mammals, is that they cannot repair the damaged central nervous system. By contrast, the zebrafish model has a remarkable ability to regenerate the brain and spinal cord after injury, due to populations of ependymoglia. Previous work has shown that for ependymoglia-driven neural regeneration to occur in zebrafish, immune cells are a key requirement. This opposes the immune response in mammals that demonstrates a prolonged pro-inflammatory phase that prevents recovery after SCI. How the activation of the zebrafish immune response results in successful spinal cord repair remains poorly characterized. In this study, we hypothesized that the inflammatory response following SCI in zebrafish is regulated by a longer anti-inflammatory response that is important for successful regeneration. By studying the spatiotemporal dynamics of immune cells post-SCI, we observed that overtime immune cells infiltrate into the injury site, correlating with a peak in proliferation of ependymoglia. Interestingly, analysis of pro- and anti-inflammatory cytokines from our initial qRT-PCR experiments suggest that anti-inflammatory cytokines remain stable across multiple time-points post-SCI in comparison to pro-inflammatory cytokines. These findings propose that in order for successful spinal cord regeneration to occur, a shorter pro-inflammatory response that is tightly controlled by anti-inflammatory cytokines is necessary.

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1-C-48: TRPM3 activation enhances mitochondrial function and provides neuroprotection in adult sensory neurons

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Peripheral neuropathy (PN) affects approximately 50% of the population with diabetes mellitus depending on age and disease severity. It is associated with substantial morbidity and is characterized by induction of pain and loss of sensory function beginning distally in the lower extremities. Recent studies suggest that molecular cascades maintaining mitochondrial function and calcium homeostasis are effective therapeutic targets for diabetic peripheral neuropathy. Interestingly, our lab has recently reported that muscarinic acetylcholine type 1 receptor (M1R) antagonists stimulated neurite outgrowth, in part, by activating Ca2+/calmodulin-dependent protein kinase kinase II (CaMKKII) and mobilization of AMP-activated protein kinase (AMPK). This further augmented mitochondrial function in sensory neurons imparting protection against neuropathy. Transient receptor potential melastatin receptor 3 (TRPM3) is a TRP type cation channel that triggers Ca2+ influx. TRPM3 is quite unique in that it binds calmodulin and is open under high phosphoinositide levels. We hypothesized that opening of TRPM3 could activate CaMKKII and induce neurite outgrowth and may mimic antimuscarinic drug effects. Dorsal root ganglion (DRG) neurons were isolated from adult control and streptozotocin-induced type 1 diabetic male Sprague-Dawley rats. Assessment of neurite outgrowth was performed in response to pregnenolone sulphate (PS) or CIM0216 (specific TRPM3 agonists, respectively). A significant dose-dependent elevation of neurite outgrowth was observed. These TRPM3 agonists also increased AMPK activation and augmented mitochondrial activity. Our investigations towards understanding of TRPM3 activation and its downstream signaling will hopefully lead to potential therapeutic targets against PN.

1-C-50: Behavioral and Neuroanatomical Alterations in CNTNAP2 Mouse Model of Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by social interaction and communication deficits and repetitive/restricted behaviors. In this study, we examine the behavioral and neuroanatomical alterations in the genetic mouse model of ASD, harboring a knockout of the contactin associated protein-like 2 gene (CNTNAP2). One of the important neuropathological features in this mouse model of ASD is the abnormal developmental migration of neurons destined for superficial cortical layers. In our study, the laminar organization of the somatosensory cortical area was analyzed by labeling with CUX-1, which is a marker for neurons normally localized to the superficial cortical layers (II-IV). Retrograde tract tracing was employed to map projections of these ectopic neurons. Behavioral analysis was conducted in mutant and control groups. By quantifying the laminar distribution of CUX-1 positive cells in the cortical area of this genetic model of ASD, we found ectopic CUX-1 positive cells in lower layers (V and VI) of cortical area as compared to the control animals. No changes were observed in co-localized CUX-1-positive and Fluorogold retrogradely labelled cells in lower layer 5 of the primary somatosensory cortex (S1) in the Cntnap2 mice compared to the WT mice. Furthermore,

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behavioral alterations were observed in mutant mice as compared to controls. In conclusion, presence of ectopic neurons in the lower layer 5 of the primary somatosensory cortex may form connections with their normal cortical targets (Cortico- cortical connections). These results suggest that neuroanatomical alterations in cortical areas could account for some core autistic behaviors.

1-C-51: Dickkopf-1 induction impairs short- and long-term structural and functional recovery after ischemic stroke.

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Stroke constitutes a major cause of death and disability of the adult population in the industrialized world. Ischemic stroke (IS), which occurs as a result of a sudden obstruction within a cerebral artery due to an embolus or thrombus, accounts for the majority of cases. After IS, it has been observed a deactivation of the Canonical Wnt pathway. Interestingly, DKK1 levels are elevated in IS brain in patients and animals' models. DKK1 inhibits the canonical Wnt pathway by preventing Wnt ligands from binding the receptor complex formed by Frizzled (Fzd) and low-density lipoprotein receptor-related protein-5/6 (LRP5/6). Wnt ligands binding to Fzd/LRP5/6 stabilizes β-catenin in the cytosol and stimulates its subsequent translocation to the nucleus to regulate transcription of target genes implicated in a wide range of physiological processes in the brain. Our study aimed to elucidate DKK1 role following IS. For this purpose, TOPGAL-iDKK1, which induce DKK1 by doxycycline administration and C57BL/6 mice were used. C57BL/6 mice were treated intraperitoneally with a DKK1 inhibitor, WAY262611 (5 and 10 mg/kg 24h after IS and every 2 days until sacrifice at 1 week) following middle cerebral artery occlusion (MCAO) which simulate IS. WAY262611 administration had reduced infarct volume and edema compared to the control mice as well as improved sensorimotor functions in a battery of behavioral tests whereas DKK1 induction impaired them. In addition, WAY262611 attenuate neuronal degeneration in treated-mice brain whereas DKK1 induction had the opposite effect. Taken together, our data suggest that pharmacological inhibition of DKK1 could be an elegant therapeutic target after IS.

1-C-52: Investigating the role of mitochondrial signaling in the maintenance of neuronal function and differentiation in the context of Parkinson's disease

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Parkinson's Disease (PD) is characterized by the degeneration of dopaminergic neurons in the Substantia Nigra leading to motor deficits. Overwhelming evidence now suggests that mitochondrial dysfunction is a key feature contributing to the pathology in PD. We have shown that mitochondrial dysfunction can alter the proliferation and differentiation of adult neural stem and progenitor cells, resulting in the dedifferentiation of newborn neurons. Using Opa1 KO as a model for mitochondrial dysfunction, we examined the mitochondrial signaling mechanisms underlying neuronal dedifferentiation. Bulk RNA sequencing was performed in differentiated neurons. We have identified a decrease in the expression of genes involved in neuronal differentiation, including those that regulate neuronal excitability and synapse formation. Using bioinformatic tools, we identified the ATF4 transcription factor as a potential

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regulator of gene expression changes following mitochondrial dysfunction. This evidence led us to hypothesize that mitochondrial dynamics signal in a retrograde manner to the nucleus to repress the expression of genes involved in neuronal differentiation, resulting in impaired neurological function. We will be identifying novel ATF4 direct targets in neurons using ChIP-sequencing and manipulating these in an effort to restore neuronal function in vitro and in vivo. Elucidating this pathway is key for understanding mechanisms underlying neurodegeneration, and will identify novel therapeutic targets by which to improve neurological function in PD. Supported by a CIHR grant to RSS. University of Ottawa.

1-C-53: Early-life immune activation is a vulnerability factor for epileptogenesis in Neurofibromatosis type 1

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Patients with Neurofibromatosis type 1 (NF1), a common multisystem neurocutaneous disorder, can develop several neurological manifestations that include cognitive impairment and epilepsy over their lifetime. Experimentally, early-life immune activation has been shown to promote later-life cognitive impairment and seizure susceptibility in normal rodents, and lead to spontaneous seizure development in some neurodevelopmental disease models. While there are reports that allude to a state of peripheral immune activation in NF1, the basal neuroimmune state in NF1 and the enduring consequences of early-life immune activation on neurodevelopment in NF1 have, until now, not been explored. In the present study, we hypothesized that early-life immune activation in NF1 promotes the development of later-life spatial memory impairments and epileptogenesis. Our results showed that whereas early-life immune activation by a systemic injection of lipopolysaccharide (LPS, 500 ug/kg) elicited a comparable cytokine response in Nf1+/- and WT male and female (p10) neonates, it promoted later-life spontaneous seizure activity only in the LPS-challenged Nf1+/- adults. In both genotypes, and irrespective of sex, early-life immune activation similarly affected adult seizure susceptibility to the GABA antagonist pentylenetetrazol and did not affect adult spatial learning and memory. Our findings suggest that early-life immune activation is a vulnerability factor for epileptogenesis in the Nf1+/- mouse and may be a risk-factor for NF1-associated epilepsy in the NF1 population.

1-C-54: Effects of neonatal hypoxia on the development of serotonergic innervation and cognitive functions

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Perinatal hypoxia is caused by prolonged oxygen deprivation to newborn infants during birth. Although the specific cellular and network changes caused by mild perinatal hypoxia (MPH) are still not well understood, this is a crucial issue since recent studies suggest that children who experienced MPH show long lasting subtle cognitive and behavioral deficits. In particular, population-based case-control studies suggested that children who experience perinatal hypoxia have a higher probability to be diagnosed with autism spectrum disorders than the general population. Serotonin (5-HT) is essential for cognitive and social functions.

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Few studies have shown that severe hypoxia-ischemia lead to reduced 5-HT neurons and innervation, however whether 5-HT dysregulations contribute to MPH-induced cognitive problems is unclear. We have recently established a mouse model of MPH, which shows long-term deficits in social interaction, attention, cognitive flexibility and memory. To investigate whether MPH affects 5-HT system development, we characterized 5-HT expression levels and innervation in the auditory and prefrontal cortex of female and male MPH mice. Preliminary data suggest both 5-HT expression and innervation complexity are reduced in adult MPH mice especially in the prefrontal cortex. We are currently investigating whether pharmacological 5-HT modulation will rescue MPH-induced cognitive impairment in adult mice. Identifying MPH effects on serotonergic system development will lead to a better understanding of how social, attention, cognitive flexibility and memory dysfunctions associated with MPH occur and may pave a path towards the development of pharmacological strategies for treating children exposed to MPH.

1-C-55: Human skin and nerve derived Schwann cells exhibit subtle transcriptomic and functional differences.

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Schwann cells (SCs) support peripheral nerve regeneration, but the efficacy of this regeneration is limited. Introducing exogenous SCs to the site of peripheral nerve injury is an ongoing avenue of investigation as a cellular therapy to enhance regeneration. Approaches that utilize an accessible source of a patient's own cells would greatly facilitate clinical translation. Previous work demonstrates that skin-derived SCs are able to promote axonal growth and remyelination in murine models of nerve injury, however, it is not clear whether skin-derived and nerve-derived SC are functionally equivalent. To this end, we isolated SCs from small skin samples and then subjected them to high resolution single-cell mRNA sequencing (scRNA-seq) followed by battery of in vitro and in vivo assays. Our genomic analyses revealed close to 95% similarity between skin and nerve SCs at differential gene level while gene network analysis showed mostly overlapping profiles between the two cell types with the exception of immune regulatory family (eg. IRF) upregulated in skin SCs. In vitro assays revealed similarity in proliferation, migration and expression of epidermal growth factor between the two cell types, which is in alignment with our genomic analysis. However, we observed subtle difference such as higher expression of VEGF and collagen content in skin SCs and higher expression of TGF-alpha in nerve SC. Overall, our results showed that skin and nerve Schwann cells share mostly identical properties with subtle differences, suggesting that skin may be a viable source of Schwann cells to improve nerve repair.

1-C-56: Role of ferroptosis in chronic-experimental autoimmune encephalomyelitis

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Ferroptosis is a non-apoptotic regulated form of cell death that is induced by iron-mediated free radicals, which trigger lipid peroxidation in the absence of sufficient levels of the antioxidant glutathione. Iron toxicity and oxidative stress play a key role in Multiple Sclerosis (MS) and Experimental Autoimmune Encephalomyelitis (EAE), an animal model used to

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study MS. We, therefore, assessed if ferroptosis plays a role in EAE. Previously, we studied the role of ferroptosis in cuprizone (CZ)-induced demyelination. We found that CZ-induced oligodendrocytes (OL) cell death was accompanied with the expression of several markers of ferroptosis. In addition, treatment with ferrostatin-1 (a ferroptosis inhibitor) prevents loss of OL and demyelination. Here, we assessed the mRNA expression of several ferroptosis markers in relapsing-remitting EAE (RR-EAE) and chronic EAE (CH-EAE). Expression of ACSF2, ACSL4, IREB2, TfR1, and NCOA4 is greater in CH-EAE compared to RR-EAE. NCAO4 is a key marker as it shuttles ferritin to autophagosomes for degradation, reducing ferritin protein and releasing bioactive iron that can trigger ferroptosis. We also found an increase in lipid peroxidation (a hallmark of ferroptosis) as assessed by 4HNE at the peak and progressive stages of CH-EAE. Importantly, treatment with UAMC-3203 (ferroptosis inhibitor) started at the peak of disease (grade3) improved clinical outcome and reduces lesion volume in CH-EAE. These results provide strong evidence that ferroptosis plays a role in CH-EAE.

1-C-57: Neuronal PTP1B hastens Alzheimer's disease in mice

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Familial forms of Alzheimer's Disease (AD) are tied to mutations in the amyloid precursor protein, but the cellular mechanisms that cause AD remain unclear. Here, we used 2 mouse models: one with amyloid beta pathology (hAPP-J20) and another with tau pathology (PS19) and asked whether activation of a phosphatase PTP1B participates in the disease process. In hAPP-J20 mice, systemic inhibition of this phosphatase using a selective inhibitor (Trodusquemine) prevented cognitive decline, neuron loss in the hippocampus and attenuated inflammation. Importantly, neuron-targeted ablation of PTP1B also prevented cognitive decline and neuron loss but did not reduce inflammation. Therefore, neuronal loss rather than inflammation was critical for AD progression in this mouse model, and that disease progression could be ameliorated by inhibition of PTP1B (Ricke et al. J Neurosci 2020, PMID: 31915254). Similarly, Trodusquemine not only prevented cognitive decline but also restored proper emotional response in PS19 mice. In summary, our preclinical studies suggests that targeting PTP1B may be a new strategy to intervene in the progression of AD. Significance: Trodusquemine is a non-competitive selective inhibitor of PTP1B. It is a natural compound isolated from dogfish liver and can pass through the blood-brain-barrier. Trodusquemine has undergone phase II clinical trials for obesity treatment, hence can be repurposed for Alzheimer's disease therapy.

1-C-58: Unveiling the role of the endolysosomal system in the pathogenesis of Parkinson's disease

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While progress has been made in understanding the neurodegenerative mechanisms that lead to cell death in Parkinson's disease (PD), early causal pathogenic events are not clear. Converging findings point at endolysosomal (EL) system dysfunction as the early mechanism

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and key pathway affected in PD. However, the exact mechanism by which alpha-synuclein (aSyn) aggregates, also called Lewy Bodies (LBs), disrupt the EL system remain elusive. To answer this question, our group created a new optogenetic-based model of PD that allows for the real-time induction of aSyn aggregates under the blue light control, mimicking all cardinal LBs features. This Light-Inducible Protein Aggregation (LIPA) system allows us to explore unsolved questions related to early interactions between the EL system, LBs and PD pathogenesis. Using the LIPA inside living cells, we were able to study the direct impact of our aggregates on vesicle homeostasis by investigating the interactions between our LIPA aggregates and the EL system using the super-resolution microscopy STED in combination with transmission electron microscopy (TEM). STED microscopy offered us a better understanding of the interactions between LBs and trafficking vesicles showing early interactions with vesicles such as the early endosomes (EEA-1) but also the degradation vesicles (LAMP1/2A) characterized by multiple co-localization with those markers. Interestingly, those vesicles were differentially interacting with aSyn aggregates overtime. The TEM realized on our purified aggregates, revealed that they are composed of multiple vesicles and shown distorted organelles. Those results allowed us to better understand how aSyn aggregates impact the trafficking of the vesicles inside the cell overtime.

1-C-59: Sex-specific profiles of m6A RNA methylation in the brain of individuals with major depressive disorder

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Introduction: Females are twice as likely to be diagnosed with Major Depressive Disorder (MDD); however, males are 3.5 times more likely to die by suicide. This is a striking example of sex differences in MDD, and mounting evidence suggests that it may be driven by sex-specific molecular mechanisms. 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 dynamic and crucial mechanism in the post-transcriptional regulation of gene expression. Among the 150 known RNA modifications, N6-methyladenosine (m6A) is the most abundant and reversible RNA modification in mammalian messenger RNA (mRNA). 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. The aim of this study is to describe the landscape of m6A in the human brain and to identify changes that may occur in the context of MDD. Methods: The ventromedial prefrontal cortex was obtained from male and female MDD and healthy control subjects. We performed m6A-seq, which allows us to detect m6A at transcripts levels. Results: We identified ~25,000 m6A peaks in the human brain, and these peaks were enriched in genes related to neuronal and synaptic regulation. Moreover, our results show a distinct m6A profile in MDD and control, with a little overlap between males and females. Conclusion: This project will help us understand the role of m6A in stress-related psychiatric disorders and will serve as a much-needed example of sex-specific analysis in psychiatric research.

1-C-60: Loss of IRF2BPL impairs neuronal maintenance through excess Wnt signaling

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De novo truncation variants in Interferon Regulatory Factor 2 Binding Protein Like (IRF2BPL) lead to a severe childhood-onset neurodegenerative disorder. To determine how loss of IRF2BPL causes neural dysfunction, we examined its function in Drosophila and zebrafish. Overexpression of either IRF2BPL or Pits, the Drosophila ortholog, impairs Wnt signaling in flies. In contrast, neuronal depletion of Pits leads to increased Wingless (Wg) expression in the brain and is associated with axonal loss, whereas genetic inhibition of wg in flies is neuroprotective in this context. Moreover, increased neuronal expression of Wg in flies is sufficient to cause age-dependent axonal loss, similar to reduction of Pits. In addition, loss of Irf2bpl in zebrafish also causes neurological defects and increased Wnt signaling. We show that the antagonistic relationship between Pits and Wg is mediated by CkIα (Casein kinase Iα) and that IRF2BPL and CKIα physically interact. Finally, WNT1 is upregulated in patient-derived astrocytes, and pharmacological inhibition of Wnt suppresses neurological phenotypes in flies and fish. In summary we provide compelling evidence that loss of Pits/IRF2BPL leads to excess Wnt in the mature nervous system and evidence that excess Wnt impairs long-term neuronal maintenance.

1-C-61: Increased expression of DISC1 restores mitochondrial axonal transport and rescues RGC function in glaucoma

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Purpose: Adequate distribution of mitochondria in retinal ganglion cell (RGC) is crucial for energy balance and synaptic function. Here, we tested the hypotheses that: i) early deficits in mitochondrial transport in glaucoma contributes to RGC loss, and ii) the adaptor protein Disrupted in Schizophrenia 1 (DISC1) is an essential regulator of mitochondrial trafficking along RGC axons. Methods: Ocular hypertension (OHT) was induced by intracameral injection of magnetic microbeads in Thy1-CFP-MitoS mice. Two-photon laser scanning microscopy (TPLSM) was used to live image mitochondrial transport along RGC axons followed by kymograph analysis. Mitochondrial adaptor genes were analyzed by qPCR using mRNA from FACS-sorted RGCs. DISC1 levels were modulated using short-interference siRNA or recombinant adeno-associated virus serotype 2 (AAV2.DISC1). RGC function was assessed by measuring optomotor responses. Results: Live imaging using TPLSM show a substantial reduction of anterograde mitochondrial transport along RGC axons soon after glaucoma induction relative to sham-injected controls (50% decrease, $p<0.001$, n=35 axons/group). Analysis of mitochondrial adaptor transcripts showed marked DISC1 reduction after OHT induction. DISC1 protein, which is abundantly expressed by naïve RGCs, was also downregulated by OHT. siRNA-mediated attenuation of DISC1 further reduced mitochondrial transport and exacerbated RGC death (14% vs. Ctl, $p<0.05$). In contrast, AAV2.DISC1 fully restored mitochondrial mobility and promoted RGC survival in glaucomatous eyes (30% vs. Ctl, $p<0.001$). AAV2.DISC1 also improved optomotor responses, indicative of RGC functional

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recovery. Conclusions: OHT triggers early mitochondrial transport deficits and limits the availability of trafficking proteins, notably DISC

1-C-62: Live two-photon calcium imaging in retinal ganglion cells: characterization of early changes in a mouse glaucoma model

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Purpose: Our current understanding of calcium (Ca) dynamics in living retinal ganglion cells (RGCs) and how they are altered in glaucoma is limited. Here, we used two-photon laser scanning microscopy (TPLSM) to investigate i) real-time light-triggered Ca responses in ON and OFF RGCs and their compartments (dendrites, soma, axons), and ii) alterations in light-evoked Ca responses during ocular hypertension (OHT) damage. Methods: Live Ca imaging in RGCs was performed by TPLSM in transgenic mice carrying the Ca indicator CGaMP6. OHT was induced by intracameral injection of magnetic microbeads. The following light-evoked Ca responses were measured: i) baseline fluorescence (F0), ii) peak fluorescence (F/F0), ii) rise time (Tr: time to reach 1/3 peak F/F0), and iv) decay time (Td: time to fall to 1/3 peak F/F0). Results: TPLSM imaging demonstrated distinct light-evoked Ca dynamics among RGC subtypes, with ON cells characterized by higher F/F0 and faster (low Tr) responses than OFF cells (N=8 mice, ~70 cells/group, $p<0.001$, $p<0.01$). TPLSM also revealed distinct compartment-dependent Ca responses including lower F0 in axons and dendrites relative to soma, and higher F/F0 in axons relative to soma (N=5 mice, ~7 cells/group, $p<0.001$, $p<0.05$). RGC Ca responses were altered soon after induction of OHT. For example, ON RGCs displayed a significant increase in Td values relative to controls (N=8 mice, ~90 cells/group, $p<0.05$), suggesting delayed Ca signal decay in glaucoma. Conclusions: Our data support that: i) TPLSM is a powerful tool to assess Ca dynamics in living RGCs, ii) Ca responses differ among RGC subtypes and subcellular compartments, and iii) Ca dynamics are altered in glaucoma indicating impaired Ca homeostasis in vulnerable RGCs.

1-C-63: Pharmacological inhibition of Polo-like kinase 2 modulates Alzheimer's disease pathology in a sex-dependent manner

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Increasing evidence suggest that phosphorylation plays an important role in the aggregation and toxicity of amyloid beta (Aβ) resulting from the amyloid precursor protein (APP) cleavage, and Tau, the major neuropathological hallmarks of Alzheimer´s disease (AD). Our laboratory has reported an accumulation of Polo-like kinase 2 (PLK2) in the brains of AD patients. Thus, the aberrant accumulation and activity of PLK2 may contribute to AD. Our goal is focused on examining the effect of PLK2 pharmacological inhibition on APP and Tau accumulation and toxicity in cells and transgenic mouse models of AD. HEK293T cells were used to examine the effect of PLK2 and its inhibition on APP and Tau protein levels by immunoblotting. In vivo, behavioral analysis incorporated evaluation of different learning and memory tasks. Biochemical and histological analysis of AD neuropathology (APP, Tau, their

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phosphorylated forms, and synaptic dysfunction) were performed using immunoblotting and immunohistochemistry. We observed that PLK2 overexpression decreases APP and Tau levels in a PLK2-concentration dependent manner, counteracted by PLK2 pharmacological inhibition in cells. In vivo, our results showed cognitive decline and AD hallmarks in symptomatic mice, as well as a decrease in some pathological aspects upon PLK2 inhibition in a sex-dependent manner, both at the behavioral and molecular levels. Overall, this project will shed light onto novel mechanisms by which phosphorylation regulates Tau and APP aggregation and toxicity, providing a novel therapeutic target for AD and related dementia.

1-C-64: Unprecedented gene expression of brain resident T-cell receptor beta and superoxide dismutase in a neurodegenerative disorder

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Abstract: Immune resident receptors like T-cell receptor β (TCR-β) subunit is known to be natively expressed on T-lymphocytes, whose gene expression was also elucidated in the mouse cerebral cortex (Syken & Shatz, 2003). However, it still remains unknown if brain resident immune proteins like TCR-β subunit expression undergo modulation under a neuropathological condition like Huntington's disease (HD). Hypothesis: TCR-β subunit expression may be upregulated in a neurological disorder like HD which may further accelerate oxidative stress and contribute to neuronal apoptosis. Methods: In this study, we used 3-nitropropionic acid (3-NP) known to mimic neuropathological symptoms of HD. We performed semi quantitative reverse transcriptase polymerase chain reaction (RT-PCR) from brain cortical samples isolated on 30th day from 4 months old male C57BL/6 mice, divided into control (intraperitoneal injection with 1X saline) and HD groups (intraperitoneal injection with 75mg/kg of 3-NP). Preliminary results: We found TCR-β mRNA was significantly upregulated by 37% in both cortical and striatal tissues taken from 3-NP induced HD mice when compared to control (n = 4; p = 0.0004, Student's t-test). Also, superoxide dismutase 1 (SOD1) expression showed a downregulation by 40% in HD mice as compared to control (n = 4; p = 0.02; Student's t-test), indicating that under oxidative stress, the antioxidant pathway in HD gets compromised. Conclusion: Overall, our data shows that combating TCRβ expression may offer a novel perspective to the function of neuronal expressed truncated immune proteins in HD disease progression.

1-C-65: Light-inducible alpha-synuclein aggregation in the midbrain impairs nigrostriatal dopaminergic transmission

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Parkinson's disease (PD) is characterized by intracellular inclusions of misfolded α-synuclein, known as Lewy bodies, and by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) that leads to dopamine (DA) depletion at the striatum. However, it remains elusive how the aggregates of α-synuclein can affect the normal function of dopaminergic projections, especially due to the absence of proper models that can reproduce the features of PD. In this context, we have recently developed an in vitro and in vivo model of PD based

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on the optogenetics technology named LIPA (light-inducible protein aggregation) that controls the aggregation of α-synuclein under the control of blue light. We showed that LIPA mimics the histopathological characteristics of PD, and allow thus to study how the aggregation of α-synuclein in dopaminergic cells of SNc can cause a progressive disruption in the nigrostriatal pathway. To investigate the physiological impact of LIPA-induced α-synuclein aggregation on the dopaminergic projections, we assessed the activity of striatal cells. Briefly, we implanted mini-endoscopes coupled with an optic fiber to induce α-synuclein aggregation in the SNc, and analyzed the neuronal activity using the calcium indicator GCaMP6s in the striatum of freely moving mice. Our results show a progressive decrease in the synchronized activity of striatal cells caused by the aggregation of α-synuclein. Altogether, our data showed that the use of this new LIPA-α-synuclein system offers a unique tool to elucidate the morphological, and physiological changes occurring in the dopaminergic projections in the context of PD.

1-C-66: Transcriptomic effects of propranolol and primidone uncover important pathways for tremor reduction in essential tremor

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Essential tremor (ET) is one of the most common movement disorders, affecting 5% of individuals over 65 years old. Despite its high heritability, few genetic risk loci for ET have been identified. Previously, drug screens have been used to uncover genes related to complex diseases, particularly for disorders with subsets for drug-responsive patients. ET notably presents patients who are selectively responsive to two tremorolytic drugs: propranolol and primidone. Genes affected by these drugs might inform us on relevant genes in ET pathophysiology. The objective of this study was thus to identify propranolol and primidone-specific, as well as convergent transcriptomic drug targets in cerebellar DAOY cells and cortical neural progenitor cells (NPCs). To achieve this, DAOY and NPC cells were treated with clinical concentrations of propranolol and primidone, followed by RNA-sequencing to identify differentially expressed genes. A meta-analysis approach was used to identify convergent genes across cell lines and treatments. Reactome and gene ontology pathway enrichment analysis identified axon guidance, vascular endothelial growth factor signalling, and endosomal sorting complex required for transport as significant. Furthermore, the expression of genes previously implicated in genetic and transcriptomic studies of ET, such as TRAPPC11, were significantly upregulated by treatment with propranolol. Our results highlight important cellular pathways by which propranolol and primidone might reduce tremor, as well as identify potential genes harbouring risk variants for ET.

1-C-67: Investigating the impact of tau deletion in a Huntington's disease mouse model

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The microtubule-associated tau protein is essential to the stabilization of neuronal microtubule networks and impaired function has been associated with disease. Indeed, tau

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hyperphosphorylation and conformational abnormalities are hallmarks of tauopathies - a subclass of neurodegenerative diseases characterized by the deposition of abnormal tau proteins in brain tissue. Accumulating evidence has suggested that tau contributes to Huntington's disease (HD) pathology - a neurodegenerative disease caused by the formation of a mutant huntingtin protein (mHtt) and characterized by motor, psychiatric and cognitive deficits. Specifically, studies have reported that (i) tau aggregates form within several brain structures in HD patients, (ii) in a transgenic HD mouse model, behaviors were improved with a tau deletion and therefore that (iii) this disease could be a secondary tauopathy. HYPOTHESIS. Tau protein could aggravate and/or accelerate the onset of behavioral and neuropathological phenotype of HD. Reducing tau expression will improve behavioral phenotype of the zQ175 mouse model of HD. METHODS. zQ175 mice were crossed with tau knockout (mTKO) mice and behavioural tests were performed at 3, 6, 9 and 12 months to assess the evolution of anxiety, cognitive and motor deficits in relation to the presence or absence of tau. RESULTS. Our preliminary results suggest that loss of tau induces a worsening of behaviors in HD mice. To understand our results, we targeted a hypothesis: mHtt can block the compensatory mechanism of tau deletion in HD mice. CONCLUSION. Based on these early findings, tau appears to play an essential role in HD. This project will contribute to a better understanding of the relationships between tau, mHtt and the development of deficits in HD.

1-C-68: Development and epileptic encephalopathy 73 - the RNF13 variants L311S and L312P alter the endolysosomal pathway.

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Developmental and epileptic encephalopathies (DEE) are rare and serious neurological disorders characterized by severe epilepsy with refractory seizures and a significant developmental delay. In 2019, DEE73 was linked to genetic alteration of the RNF13 gene, which converted positions 311 or 312 in the RNF13 protein from leucine to serine or proline, respectively (L311S and L312P). Specifically, three unrelated individuals were reported to carry de novo heterozygous mutations with clinical features including but not limited to feeding difficulties, failure to thrive, restlessness, abnormally increased muscle tone, refractory epilepsy, cortical visual impairment, bilateral hearing loss, limb contractures, scoliosis, microcephaly, and profound intellectual disability. Currently, knowledge is mostly limited to the genetic and phenotypic alterations themselves rather than the molecular and cellular mechanisms affected by RNF13 protein variants. Using a fluorescence microscopy approach, the current study shows that RNF13 wild type localizes extensively with endosomes and lysosomes while L311S and L312P presence in lysosomes is reduced in HeLa cells. Besides, our results show that RNF13 L311S and L312P proteins affect the size of endosomal vesicles along with the temporal and spatial progression of fluorescently labeled epidermal growth factor and transferrin in the endolysosomal system. Importantly, our study provides a first step toward understanding the cellular and molecular mechanism altered by DEE73-associated genetic variations of RNF13.

1-C-69: Extracellular vesicles: a window into the etiology of major depressive disorder

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Major Depressive Disorder (MDD) is one of the leading causes of disability worldwide. MicroRNA's (miRNA) are well known epigenetic regulators that are disrupted in MDD and are packaged into extracellular vesicles (EVs). EVs have emerged as means of intercellular communication, transferring miRNA, as well as other molecules such as proteins between cells, altering cell function in recipients. Therefore, we hypothesize that EV cargo from the anterior cingulate cortex will have a disease specific profile that could mediate disease development in MDD subjects compared to healthy controls. EVs were isolated from post-mortem human brain tissue using size exclusion chromatography. The quality was assessed by western blots and transmission electron microscopy (TEM). RNA was extracted and sequenced using the Illumina Platform. Proteins were also extracted and profiled using LC-MS/MS. Western blots showed no contamination with cellular debris, along with enrichment of the exosomal marker CD9. TEM images showed vesicles mostly between 30 and 200 nm in size. Preliminary differential analyses revealed that both the miRNA and proteomic profiles of the EVs are dysregulated in MDD. This will be the first study to profile brain-derived EV miRNA and protein in the context of depression. Future studies will be needed to determine the effect of the dysregulated EV cargo in MDD. This could provide novel mechanistic insights into the potential role of EVs in the pathophysiology of MDD, which could be a starting point for the development of targeted therapeutic strategies and prevention measures.

1-C-70: Neuronal potassium - chloride cotransporter KCC2 function is impaired in the indirect pathway of the basal ganglia in Huntington's Disease

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Huntington's disease (HD) is an inherited disorder, characterized by progressive motor dysfunction resulting from degeneration of the striatum. The striatum consists of two major pathways: the direct and indirect, which promote and inhibit movement, respectively. The indirect pathway is known to degenerate earlier in HD, though the cause of this enhanced susceptibility remains unclear. Accumulating evidence suggests that impaired synaptic inhibition may underlie this specific pattern of degeneration. Synaptic inhibition in the mature brain is mediated by GABA, which exerts fast hyperpolarizing inhibition by binding to Cl- -permeable GABAA receptors. GABAergic inhibition requires low intracellular Cl- concentration ([Cl-]i), which is maintained by potassium-chloride cotransporter 2 (KCC2). When KCC2 function is reduced, [Cl-]i increases, consequently weakening synaptic inhibition. Using electrophysiology, we determined that KCC2 function was reduced in the indirect pathway of early symptomatic HD mice, as indicated by a depolarization in the reversal potential for GABA. Interestingly, this reduction in KCC2 led to GABA-mediated excitation in the Globus Pallidus externa, the output structure of the indirect pathway. In addition, pharmacological reduction of [Cl-]i with bumetanide delayed the onset of motor impairments in HD mice. This work demonstrates that impaired GABAergic inhibition in the indirect pathway plays a key role underlying circuitry and motor defects in HD, whereby Cl- regulation may serve as a potential therapeutic target in the treatment of HD.

1-C-71: Repetitive mild traumatic brain injuries induce sexually dimorphic behavioral deficits, immune cell infiltration and microglia dynamics in adolescent mice.

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Adolescents are susceptible to repetitive mild traumatic brain injuries (RmTBIs) which can cause compounding, sexually dimorphic neurological deficits with potentially devastating impacts on brain development. Neuroinflammation accompanies RmTBIs but the impact of sex-specific neuroinflammation during adolescent RmTBIs has been understudied. Here, using a lateral impact model of RmTBI to mimic the biomechanical forces experienced in humans, we subjected adolescent male mice to RmTBIs at 24-h intervals and quantified behavioral deficits, and brain volumetric and structural changes by MRI. Five RmTBIs caused significant motor deficits, increased brain volume in multiple brain regions and reduced white matter integrity in the corpus callosum. We then compared behavioral deficits in adolescent male and female mice and observed sex-specific deficits in motor function, whereas both sexes had memory deficits. Flow cytometry revealed time- and sex-dependent infiltration of macrophages and T cells and male-specific decreases in microglia number, which was confirmed with immunohistochemistry. We show novel neuroinflammatory responses after adolescent RmTBI, as well as sex differences in behavioral deficits that expands the current understanding of RmTBI pathophysiology in this neurodevelopmental period. Pannexin-1 channels are ubiquitously expressed in the brain and may play a role in neuroinflammation after RmTBIs. We are currently using a myeloid-specific Panx1 knockout mouse line to investigate the effects on behavioral deficits and neuroinflammation after adolescent RmTBIs.

1-C-72: Mass spectrometry imaging of gangliosides in Alzheimer's Disease

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Lipid dysregulation is a core component of neurodegeneration in Alzheimer's Disease (AD). Gangliosides are members of the glycosphingolipid family enriched in the central nervous system. The healthy brain maintains a homeostatic balance of gangliosides. GM1, the most abundant ganglioside in the adult brain, is enriched within neuronal membrane rafts and exerts neuroprotective effects. In contrast, accumulation of GM2 and GM3, degradative by-products of GM1, can directly cause neurodegeneration, suggesting that ganglioside dysregulation is a key contributor in AD pathology. Our current gap in knowledge is whether ganglioside dysregulation is worsened by, or contributes, to beta-amyloid (Aβ) accumulation in the brain. Thus, anatomical-specific distributions of gangliosides were investigated in the amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mouse model of AD that develops age-dependent Aβ plaques. Hypothesis: Aβ accumulation leads to increased levels of simple gangliosides GM2 and GM3 contributing to neurodegeneration in the AD brain. Methods: Matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) was performed on brains of wildtype and transgenic mice aged 4, 8, 12, and 18 months to quantify ganglioside distribution across anatomical regions. Results: Our data demonstrate an age-dependent increase in simple gangliosides that are exacerbated in the Tg mice. Aged Tg mice showed higher levels of simple gangliosides as compared to Wt in the cortex and hippocampus, brain regions of initial amyloid deposition. Significance: This work identifies a potential interplay between Aβ and simple gangliosides in driving

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neurodegeneration, highlighting a rationale for evaluating glycosphingolipid modifying approaches in AD treatment.

1-C-73: Synaptotagmin-1 in postmortem hippocampus: implications for the pathological and clinical diagnoses in older adults

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Synaptic deficits strongly correlate with cognitive impairment and contribute to the severity of depression in elderly persons. Specific presynaptic proteins are associated with better cognitive performance. Synaptotagmin-1 (STG) is a synaptic calcium sensor that regulates neurotransmission. Currently, it is unknown whether STG isoforms are associated with cognition and depressive symptoms in the elderly. The objectives of this study were to quantify STG isoforms in human hippocampus and evaluate their associations with cognitive function, and to assess the relationship of the STG isoforms with the likelihood of depressive symptoms. Human brain samples (n = 294) were obtained from the Rush Memory and Aging Project, which is a community-based study. Hippocampal levels of the STG isoforms were evaluated by immunoblotting. A monoclonal antibody recognized full-length STG (65 kDa) and two fragments that were of a high (40 kDa) and low (37 kDa) molecular weight. Lower 37 kDa synaptotagmin levels were found in participants with severe Braak stage (V-VI), defined as tau pathology, than those at a moderate Braak stage (III-IV) (-21%). After adjusting for the demographics and age-related neuropathologies, global cognition was associated with 37 kDa STG levels but not the 65 and 40 kDa STG proteins. Each unit increase of the 37 kDa STG was associated with lower odds of dementia (P=0.039). Adjusted binary logistic models showed that higher levels of the 65 kDa STG was associated with a lower likelihood of having depressive symptoms (odds ratio=0.64, P=0.01, 95% CI=0.46-0.89). Neither of the STG fragments were related to depressive symptoms in this subset of the subjects. These findings reveal that STG isoforms have different associations with disorders in the aging hippocampus.

1-C-74: Investigating the contribution of tau to Huntington's disease pathology

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The tau protein implicated in microtubule stabilization exists in six isoforms resulting of alternative splicing of the tau gene. In several conditions collectively referred to as tauopathies, tau becomes hyperphosphorylated and accumulates into various pathological forms. It has been recently reported that the expression of 4R tau isoforms is increased in patients with Huntington's disease (HD), suggesting that this disorder may be a secondary tauopathy. We hypothesize that the introduction of tau to cell and animal models of HD leads to an exacerbation of intracellular huntingtin (HTT) aggregation with consequences on cellular and behavioral functions. Human synthetic recombinant tau is introduced to an HD neuronal cell line (StHdh cells) and various aspects of toxicity are assessed. The uptake of tau is observed by immunocytochemistry, metabolic activity using an MTT assay and HTT

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aggregation is measured by filter retardation assays. To evaluate the influence of tau on behavioral impairments, 3-month old wild-type and HD (zQ175) mice received intracerebral stereotaxic injections of tau into the hippocampus and prefrontal cortex and several behavioral tests were performed. Low dose tau fibrils significantly decrease the metabolic activity of healthy and HD cells while the 3R forms of tau increase HTT aggregation in the HD cells. In vivo, 4R monomers and 3R fibrils exacerbate behavioral phenotypes in WT mice notably anxiety-like behavior; whereas 4R monomers tend to worsen cognition in zQ175 mice. Although preliminary, tau seems to alter cellular features associated to HD and worsen behavioral phenotypes in mice. Ongoing experiments will allow us to link the cellular alterations to the behavioral aspects observed, shedding light on the role of tau in this disease.

1-C-75: Lost neural heterogeneity in human epilepsy is a fundamental principle unifying epileptic etiologies

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Many pathological changes associated with epilepsy can be recast as decreases in cell and circuit heterogeneity. We hypothesize that epileptogenesis can be recontextualized as a process where reduced cellular heterogeneity renders neural circuits less resilient to seizure-like transitions, for which we provide experimental, computational, and mathematical support. Patch clamp recordings on human cortical pyramidal neurons from resected epileptogenic and non-epileptogenic tissue revealed a significant decrease in heterogeneity in intrinsic neuronal excitability amongst epileptogenic neurons. In a computational spiking excitatory-inhibitory (E-I) cortical neural network, networks with epileptogenic heterogeneity levels were uniquely vulnerable to ictogenesis-like sudden transitions into a synchronous and hyper-active state. These dynamics were explained via mathematical analysis of the corresponding mean-field system, revealing a unique bifurcation structure in networks with low heterogeneity. Interestingly, experiments also revealed a surprising decrease in single-cell excitability, quantified via the frequency-current (FI) relationship, in epileptogenic neurons, which can be explained by the mathematical consequences of decreased heterogeneity on input-output relationships. This interdisciplinary study represents the first investigation of the role of neural heterogeneity in epilepsy, experimentally identifying decreased heterogeneity associated with the disease and computationally and mathematically connecting it to the onset of seizure-like dynamics.

1-C-76: Role of the endocannabinoid system in stress resilience and depression: a master regulator of neurovascular health

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Only 30 to 50% of major depressive disorder (MDD) patients completely remit, making it a leading cause of disability worldwide. This lack of efficacy suggests that current neuron-centric treatments do not address important biological factors. Chronic stress, the main environmental risk for MDD development, has been known to trigger a whole-body response

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including neuroimmune and neurovascular adaptations. We recently reported that chronic social stress causes a detrimental increase in blood-brain barrier (BBB) permeability, promoting infiltration of circulating inflammatory mediators and development of depressive-like behaviours 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. Interestingly, the endocannabinoid system (ECS) is a crucial regulator of stress responses. Moreover, ECS was shown to regulate BBB permeability under homeostatic and pathological conditions. Here we combine molecular, cellular and morphological analyzes to behavioral studies and show that the ECS is actively involved in stress resilience to chronic social defeat stress, a mouse model of depression, in a sex- and brain region-specific manner. Based on those results, we propose that stress-induced increased in BBB permeability could be due to pathological changes in the ECS system, enabling release of inflammatory signals into the circulation, vascular dysfunction and establishment of depressive behaviours.

1-C-77: Endogenous cerebellin 1 prevents amyloid-β oligomers accumulation in the cerebellar granule cells

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Amyloid-β (Aβ) is a key molecule involved in the pathogenesis of Alzheimer's disease (AD), the most common neurodegenerative disease. Earlier researches have showed that amyloid deposition in the cerebellum only occurred in late stage of AD. Furthermore, cerebellar neurons are resistant to the neurotoxic effects of Aβ oligomers (AβOs). Interestingly, we have previously identified that AβOs bind to the alternative splicing site 4 (SS4) of neurexins (NRXs). NRXs are presynaptic molecules that orchestrate synapses development in the brain by engaging with several ligands to form extracellular protein networks. Among those ligands, cerebellin 1 (Cbln1) promotes synapse formation in the cerebellum by bridging NRX and postsynaptic GluD2. Interestingly, Cbln1 binds to NRXs through the SS4, the same domain responsible for AβOs interaction. We thus hypothesize that endogenous Cbln1 is preventing AβO accumulation in cerebellum by blocking the interaction between AβOs and NRX. Indeed, our results revealed that treatment with soluble Cbln1 completely abolished the binding of AβOs to NRX-expressing COS7 cells. Interestingly, application of AβOs did not interfere NRX-Cbln1 binding suggesting that NRX-Cbln1 complex is resistant to AβOs. Furthermore, AβOs treatment in Cbln1 KO cerebellar neurons showed a significant increase of AβOs deposition on axons compared to wild-type neurons suggesting that endogenous levels of Cbln1 could protect cerebellum neurons in AD. This study may uncover a new mechanism that promote selective cerebellar resistance to Aβ-induced pathological mechanism in AD.

1-C-78: The temporoammonic (TA) input to CA1 synapse is hyperexcitable in MeCP2 -/Y mice

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The temporoammonic (TA) pathway provides input directly from layer III of the entorhinal cortex (ECIII) to the distal dendrites of CA1 pyramidal cells in the stratum lacunosum-moleculare (SLM) of the hippocampus. The TA synapse influences the firing of CA1 pyramidal neurons and modulates the flow of information to the hippocampus. Neurons in ECIII are degenerated in Rett Syndrome (RTT), thus the aim of this study is to investigate how the presence of the MeCP2 mutation alters properties of the TA-CA1 synapse using electrophysiological characterization of synaptic and network connectivity. Electrophysiological neuronal properties were assessed by making whole-cell patch clamp recordings. The SLM neurons in Mecp2-/Y mice were found to be hyperexcitable showing increased action potential firing rate, with a significantly larger sag potential and post inhibitory rebound potential observed compared to matched wild-types. Additionally, evoked EPSCs of CA1 pyramidal neurons were significantly larger when the TA-CA1 pathway was stimulated, with no change in evoked IPSCs compared to wild-types. Moreover, the reversal potential for GABA (EGABA) was measured using a high intracellular chloride concentration (30mM) and found to be depolarized compared to wild-types controls. Finally, to assess network connectivity we examined hippocampal long-term potentiation induction and paired pulse ratio which were both found to be unaffected in TA-CA1 pathway in the MeCP2-/Y mouse. Taken together, the data demonstrates increased intrinsic excitability of the CA1 pyramidal neurons, revealing a potential mechanism of changes in GABA activity and provide preliminary evidence suggesting that targeting this phenotype may rescue neuronal abnormality and disease progression.

1-C-79: Depression-associated cell-type specific molecular changes in the post-mortem dorsolateral prefrontal cortex

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Cell-type specific techniques empower investigation of disease-associated molecular changes within finely defined cell-types or states. These techniques could further elucidate the mechanisms underlying MDD (major depressive disorder), which involves distinct neuronal, astrocytic, oligodendroglial, microglial, and endothelial contributions. Moreover, the molecular phenotype of MDD is sexually dimorphic, providing a strong impetus to study both males and females. We previously performed single-nucleus RNA-sequencing (snRNA-seq) in the post-mortem dorsolateral prefrontal cortex (dlPFC) in a cohort of male subjects who were either psychiatrically healthy or were depressed and died by suicide. We found that a subtype of deep layer excitatory neurons and immature oligodendrocyte precursor cells showed the highest numbers of differentially expressed genes (DEGs). We focused on the excitatory neuronal subtype, identified genes which are highly expressed within it, confirmed that it can be stably detected across independent snRNA-seq datasets, and optimized a protocol for sorting this population from the post-mortem brain for future DNA methylation studies. Further, we expanded our snRNA-seq cohort to include depressed female subjects who died by suicide and matched controls. We recapitulated the cell subtypes previously identified in the male cohort and identified cell-type specific DEGs within the female dataset. Future work will include meta-analysis of results from the male and female cohorts and investigation of epigenetic changes within isolated cell subtypes of interest.

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1-C-80: Characterization of the interaction between pathological α-synuclein aggregates and the synaptic cell adhesion molecule neurexin

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Synucleinopathies are a group of neurodegenerative diseases that imply the pathological aggregation of alpha-synuclein (α-syn), a presynaptic protein supposedly involved in regulating synaptic vesicles exocytosis. It is clear that pathological aggregation of α-syn within neurons leads to neuronal defects and ultimately to neuronal death. Accumulating evidence show that synaptic dysfunction occurs early in the disease, well before neuronal death. Additionally, pathological α-syn is able to spread between cells in a prion-like manner, suggesting synaptic mechanisms would be involved in α-syn spreading. However, what mechanisms are responsible for synaptic dysfunction and α-syn spreading remain unclear. We performed a screening of neuronal transmembrane proteins and revealed neurexin (NRX) as an interactor of α-syn aggregates. NRXs are important presynaptic adhesion molecules that regulate synaptic differentiation and transmission. Therefore, we hypothesized that the interaction between NRXs and α-syn contribute to early synaptic dysfunctions observed in synucleinopathies. So far, our work shows that pathological α-syn specifically interacts with β-isoform of NRX at nanomolar range. Next, we will focus on the consequences of this binding by testing synapse differentiation, surface level of NRX and interaction with its endogenous ligands. The result of this project might improve our understanding on synaptic molecular mechanism associated with pathological α-syn and lead to the development of therapeutics delaying the neurodegeneration by preventing synaptic dysfunctions.

D - Sensory and Motor Systems

1-D-81: Pain synesthesia as a trigger for pain in pre-sensitized regions of healthy undergraduates

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Pain synesthesia is an extreme form of empathy where an individual can personally feel the pain of another within their own body. The experience of pain synesthesia has been noted in populations who have experienced physical trauma (acquired synesthesia). Pain synesthetes typically experience pain in a pre-sensitized region of the body (i.e., a previously broken leg), when observing or imagining others in pain. However, the influence of social factors, such as perceived social support and adverse childhood experiences have not been explored in pain synesthesia. In this experiment, 137 healthy undergraduate students were asked to complete a series of questionnaires to assess various social and psychological factors along with past pain experiences (e.g., Multidimensional Scale of Perceived Social Support, Post-Traumatic Stress Diagnostic Scale, West Haven-Yale Multidimensional Pain Inventory, etc.). Participants were then shown a series of coloured photographs displaying right hands and right feet in painful versus non-painful scenarios. Participants were asked to rate each image

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for perceived pain experienced by the scenario and whether the images triggered synesthetic pain. The results will help us understand whether social factors influence individual susceptibility to synesthetic pain and whether viewing still images of hands and feet trigger synesthetic pain in pre-sensitized regions.

1-D-82: Sympathetic preganglionic neuron innervation by locomotor related V3 spinal neurons

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[1]University of Manitoba

In Canada, 80000 people live with spinal cord injury (SCI), with roughly 1400 individuals added to this population each year. These individuals live with lost motor function, multiple secondary complications and disuse-related diseases that arise from severe inactivity imposed by the injury. Dysregulation of the sympathetic nervous system is common in SCI individuals as connections between the autonomic command centres in the brainstem are severed from spinal sympathetic preganglionic neurons (SPNs) that regulate sympathetic outflow. SPNs are found in intermediate lamina and central autonomic nuclei of T1-L2 spinal cord and depending on the site of injury, some or all sympathetic activity is affected, such as hindering the ability to sweat or increase energy metabolism to meet increased metabolic demands of the body. Recently, epidural stimulation has been shown to restore voluntary movements in people with SCI and improves autonomic function. However, the neurons and neural pathways that allow for both locomotor and autonomic function recovery are unknown. We hypothesize that ventrally derived propriospinal interneurons (INs) that are involved in locomotion, and are termed V3 INs, relay ascending motor commands to SPNs to ensure adequate sympathetic activity during increased metabolic demands such as locomotion. Our preliminary data has demonstrated that lumbar V3s project to and synapse throughout the IML of thoracic spinal cord. Our continuing work focuses on if there are greater V3 synaptic densities innervating the heart region of the thoracic spinal cord (T1-T5).

1-D-83: Larynx motor representation in fruit bats located with intracortical microstimulation (ICMS) optimized for detection of weak electromyographic (EMG) signals

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Bats exhibit several traits associated with human communication, including vocal learning and complex social communication--traits that are rare among mammals. Here, we use a bat model to investigate the cortical representation of the larynx to begin studying the motor control of complex vocal behaviours. In anesthetized Egyptian fruit bats (Rousettus aegyptiacus), we applied ICMS to the frontoparietal cortex to evoke muscle contractions. We tested for the presence of a larynx representation in M1, S1, and adjacent cortex by recording electromyographic (EMG) activity from the cricothyroid muscle in the larynx. In order to correct for EMG artifacts introduced by the ICMS signal itself, we systematically varied ICMS circuitry (e.g. return lead placement, current sense resistor) to minimize contamination. This method also reduces the need for "blanking" techniques, which can lead to signal loss. Our corrections reduced the artifact by ~90% and increased the EMG signal-

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to-noise ratio, providing a robust laryngeal signal. Here we report ICMS activation of the larynx at two rostromedial sites in M1--each of which had a distinct latency (20 vs 190 ms)--in a case study of Rousettus. Ongoing experiments will focus on denser mapping of this region to determine whether latency differences reflect modules within M1 or distinct cortical fields, perhaps with different roles in the control of vocal behaviour.

1-D-84: Using auditory brainstem responses to evaluate the ultrasonic hearing abilities of the domestic cat

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The upper hearing limit of humans is 20kHz, and sounds having frequencies above 20kHz are considered ultrasonic. Ultrasonic frequencies are important to a variety of species, many of which have a well-defined and much higher hearing limit compared to humans. A common model used for auditory research is the domestic cat (Felis catus). Even though it is generally accepted that cats can hear ultrasonic frequencies, there are notable discrepancies in the literature regarding the full extent of the cat's hearing abilities. Here, auditory brainstem responses (ABRs) are used to evaluate the ultrasonic hearing abilities of cats. The ABR is an objective test used to assess the physiological integrity of the auditory pathway from the cochlea up through the brainstem. Wideband stimuli (clicks) as well ultrasonic pure tones are presented to the subject. Each stimulus leads to electrical responses that reflect the neurophysiological activity in the auditory nerve and the auditory nuclei in the brainstem. This work evaluates the amplitude and latencies of the ABRs to the different stimuli presented. Since cats are a common animal model in hearing research, it is crucial to validate and expand our current understanding of their hearing abilities. By using ABR data in conjunction with data from psychoacoustic experiments to investigate specifically the ultrasonic hearing abilities of cats, we can elucidate uncertainties and ultimately better our understanding of brain regions responsible for the cat's ability to perceive these high frequency signals. Supported by a grant from NSERC.

1-D-85: Poisson-Wiener prediction of neuronal temporal modulation in primary auditory cortex of the awake cat

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Compromised auditory temporal processing is predictive of impaired speech and language comprehension. Temporal modulation transfer functions (tMTFs), descriptions of the sensitivity of auditory neurons to fluctuations in amplitude over time, can be used for the diagnosis and prognosis of auditory neuropathologies. Despite being uncertain, studies suggest that a system identification method, Poisson-Wiener theory can be applied to biologically relevant sounds which often differ based on their temporal patterns, such as speech and other conspecific communication. To assess the predictability of the model in the awake auditory cortex, extracellular recordings of primary auditory cortex neurons in response to periodic click trains, Poisson clicks and conspecific vocalizations (purring) were obtained from chronically implanted cats (n=2). For each neuron, Poisson-Wiener kernels were derived and used to estimate peristimulus time histograms (PSTHs), rate modulation transfer functions (rMTFs) and tMTFs specific to that unit. Our preliminary findings show that

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second order predictions provide an improved fit compared to first order predictions. The results suggest the model has the potential to accurately estimate the auditory temporal processing of natural sounds. However, a higher order kernel is needed to capture the non-linearities present in the auditory system. Following successful application to the prediction of conspecific communication, extension of the model to humans has the potential to provide a more efficient and accurate assessment of temporal processing than currently used clinical measures.

1-D-86: Grey matter thickness in deaf cats measured using ultra-high field MRI

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Grey matter thickness derived from high-resolution magnetic resonance images is a useful non-invasive method of characterizing an interesting property of the cerebral cortex. When combined with an atlas of the species in question, these measurements can be used to distinguish anatomically relevant regions of thinning or thickening in an experimental or disease group from healthy controls. In this investigation we sought to determine if ultra-high field MRI could be used to uncover differences in thickness between the brains of deaf cats and those of hearing controls. In this study we scanned 29 control hearing and 26 deaf cats at 0.5mm isotropic resolution to look for areas of differing thickness using regions from a cat brain atlas. Thickness maps were obtained using the Advanced Normalization Tools software package and these maps were later processed in MATLAB. Two cortical regions differed significantly in thickness between the two groups, with PLLS in the right hemisphere and pPE in the left hemisphere being thicker in the deaf group. These two regions are multimodal regions of the visual and auditory system, respectively, and show that there may be evidence of cross-modal plasticity occurring in the brains of the deafened cats that manifests as thickness changes within these regions. Previous behavioral work has already suggested functional plasticity in a subset of auditory regions, and the methods used in the present study may be used in the future to determine regions of interest for future work. Supported by a grant from CIHR.

1-D-87: Microstructural alterations in grey and white matter following early-onset deafness in the cat

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Following sensory deprivation, compensatory plasticity underlies the reorganization of sensory-specific brain areas to process remaining modalities. For instance, following visual deprivation, higher order visual areas adapt to process tactile stimuli, providing somatosensory enhancement to visually-deprived individuals. Considering the consequence of plasticity following visual deprivation, what changes occur throughout the brain following auditory deprivation? Previous studies have examined microstructural consequences of deafness, including its effect on cerebral water diffusion through diffusion tensor imaging (DTI). However, nearly all investigations have studied these neuronal changes in humans rather than animals. The purpose of the present study was to extend microstructural investigations to animal models of deafness, comparing diffusivity scalars between hearing (n=27) and deaf cats (n=19) via DTI within 155 grey and 21 white matter regions. Results

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indicate structural plasticity throughout the deaf brain, indicated by a change in scalar value - generally by an increase in axial, radial and/or mean diffusivity in deaf felines compared to hearing. Grey matter regions affected in the cat include the perirhinal cortex and frontalis agranularis, and white matter tracts affected include the corpus callosum, superior longitudinal fasciculus, and more. Overall, this is the first study to examine DTI alterations following auditory deprivation in cats and it demonstrates that early-deafness incites alterations throughout the brain well beyond auditory cortex. Supported by a CIHR grant.

1-D-88: Combining the effects of cortical and spinal stimulation to improve walking after spinal cord injury

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Spinal and brain stimulation approaches are complementary in the treatment of motor disorders related to spinal cord injuries (SCI). Nevertheless, no study has directly compared their single and combined effect over immediate modulation of walking. To address this unmet need, we developed a neuroprosthesis that allows stimulating the brain and spinal motor circuits in phase-coherence with walking. Six rats were implanted with electromyographic electrodes (EMGs) within hindlimb muscles, a multi-electrode array within the hindlimb motor cortex and epidural electrodes over the lumbar (L2) and sacral (S1) spinal segments. After obtaining baselines for kinematics/EMGs on a treadmill, rats received a spinal hemisection at T9 that paralyzed one leg. The immediate effects of cortical and/or spinal stimulation over treadmill locomotion were evaluated in the intact state and after SCI. We characterized the effect of stimulation parameters such as stimulus amplitude, frequency, and duration. Gait analysis demonstrated that each stimulation technique independently modulated walking. Both cortical and L2 stimulation, when delivered in synchrony with foot lift, increased leg flexion. S1 stimulation, when delivered 80ms after the foot lift, increased leg extension. Combined cortical and spinal stimulation approaches resulted in maximal increase in foot clearance, step height and swing velocity, before and after SCI. These experiments demonstrated that cortico-spinal neuroprosthesis has the potential to reduce motor deficits and enable targeted rehabilitation protocols after SCI.

1-D-89: Reduced inhibition in depression impairs stimulus processing in human cortical microcircuits

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Cortical processing depends on finely-tuned excitatory and inhibitory connections in neuronal microcircuits. Reduced inhibition by somatostatin-expressing interneurons is a key component of altered inhibition associated with treatment-resistant major depressive disorder (depression), which is implicated in cognitive deficits and rumination, but the link remains to be better established mechanistically in humans. Here, we tested the impact of reduced somatostatin interneuron inhibition on cortical processing in human neuronal microcircuits using a data-driven computational approach. We integrated human cellular, circuit and gene-expression data to generate detailed models of human cortical microcircuits in health and depression. We simulated microcircuit baseline and response activity and

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found reduced signal-to-noise ratio and increased false/failed detection of stimuli due to a higher baseline activity in depression. Our results thus applied novel models of human cortical microcircuits to demonstrate mechanistically how reduced inhibition impairs cortical processing in depression, providing quantitative links between altered inhibition and cognitive deficits.

1-D-90: Optogenetic activation of glutamatergic neurons in the cuneiform nucleus controls locomotor speed without preventing braking or turning maneuvers in mice

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Coordinating speed and steering is essential to navigate the environment. Speed is controlled by the Mesencephalic Locomotor Region (MLR), which generates forward motion by symmetrically activating a set of reticulospinal neurons. Recent studies uncovered that steering is controlled at least in part by distinct reticulospinal neurons controlled by the superior colliculus, which processes visuomotor transformations. Whether animals can brake and turn during ongoing MLR stimulations is poorly documented. Using in vivo optogenetics, we show that mice can brake and turn during stimulation of the cuneiform nucleus, a subpart of the MLR. Using deep learning-based movement analysis, we show that the footfall pattern and limb kinematics are normal during optogenetically-evoked locomotion. We also show that increasing laser power increased locomotor speed. In the open field arena, mice could perform sharp 90° turns when approaching a corner during stimulation of the cuneiform nucleus. Turns were associated with a slowdown that was scaled to the locomotor speed when entering the corner. Mice used less sharp turning angles at faster speeds. Our results indicate that the animal could integrate environmental cues during MLR-evoked locomotion to adjust speed and motion direction, thus ensuring smooth navigation. Our study suggests that stimulation of the cuneiform nucleus may be a relevant clinical target to improve locomotor performance without restricting the ability to perform braking and steering maneuvers in pathological states such as Parkinson's disease.

1-D-91: Variability of individual responses to 30 Hz intermittent theta-burst transcranial magnetic stimulation.

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Objectives Theta burst stimulation is known to lead to lasting modulation in corticospinal excitability (CSE) but, individual responses can vary substantially. Here, our goal was to determine whether a modified intermittent TBS protocol (iTBS) consisting of 30 Hz bursts at a 6 Hz interval would lead to more consistent modulation in CSE. We were also interested in examining whether individual differences in the recruitment of indirect waves (I-waves) could predict responses to iTBS. Methods Participants (n=19) underwent single-pulse TMS to determine MEP amplitude at baseline. MEPs were also evoked using different coil orientations (AP, LM and PA) to measure differences in latency and assess I-wave recruitment. The 30 Hz iTBS intervention was then administered to the left motor cortex (600 pulses @ 80% active MT), and MEPs were reassessed at 5, 20 and 45 mins post. Results Most participants exhibited the expected MEP facilitation (13/19) post iTBS with significant

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effect detected at 20 and 45 min. Interestingly, variations in AP-LM latency differences were inversely related to iTBS responses, small differences being associated with greater facilitation. Conclusions The 30 Hz iTBS elicited robust facilitation in most participants. Contrary to previous reports, only individuals in which TMS could recruit early I-waves showed facilitation. Significance These findings suggest that 30 Hz iTBS may provide an alternative to improve the consistency of responses and that recruitment of early I-waves might be important in mediating the effects of 30 Hz vs. 50 Hz protocols.

1-D-92: Sound-induced flash illusion in forced-choice and go/no-go tasks

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The sound-induced flash illusion (SIFI), the misperception of flash number when presented with an incongruent number of clicks, has been studied almost exclusively using a forced-choice task. Compared to forced-choice tasks, Go/No-Go tasks remove the need for response selection. Understanding the audiovisual interaction under different cognitive loads will pave the way for studies in different development trajectories (e.g. cochlear implant). The task was to discriminate 1 vs. 2 flashes of Gabor stimuli at threshold contrast while ignoring the sound of clicks (0, 1 or 2). Participants were told to make two-alternative forced-choice 2AFC (i.e. left-for-1 and right-for-2) or Go/No-Go responses (either Go-for-1 or Go-for-2) in three separated blocks with order counterbalanced between participants. In all conditions, participants reported more "two-flash" in 2-click trials and vice versa in 1-click trials, when compared to 0-click trials. Furthermore, the effect in 2-click trials was larger in the Go-for-1 task compared to the Go-for-2 and 2AFC tasks. The effect in 1-click trials did not differ among tasks. Repeated measures model indicates that both click number ($F_{1,19}=42.06$, $p<.001$) and task type ($F_{1,19}=38.00$, $p<.001$) have significant impacts on accuracy. Despite the SIFI being established for 20 years, there has yet to be a departure from the forced-choice task design measuring the illusion. The differences in SIFI effect based on different task designs show that how the illusion is measured can affect the outcome. The basis for this difference is the subject of future work.

1-D-94: Investigation of darkness-induced modification of NMDA receptors within the primary visual pathway

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During early postnatal development the visual system exhibits a heightened capacity for neural plasticity in which the structure and function of neural circuits can be modified by changes in visual experience. The composition of the N-methyl-D-aspartate receptor (NMDAR) plays a major role in regulating the capacity for neural plasticity by altering the threshold for synaptic modification. The current study was designed to examine the role that the NMDAR subunit composition plays in the enhancement of plasticity that results from brief immersion in complete darkness. A novel method employing multiplex immunolabeling was developed to quantify NMDAR subunit composition in thin tissue slices from the cat visual system. This approach preserves in situ protein distribution and permitted an investigation of layer-specific receptor changes. Receptor subunit composition was examined in a group of age-matched normal control cats, as well as cats that were exposed to a short (10 day)

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period of darkness to eliminate visually-driven activity and enhance plasticity capacity. We found that darkness shifted NMDAR subunit composition toward the neonatal isoform in both visual cortex and the lateral geniculate nucleus. This was a generalized shift observed across cortical and thalamic layers. These results further implicate modifications of the NMDAR subunit composition, stimulated by reduced neural activity, as a factor underlying the enhancement of plasticity linked to dark immersion.

1-D-95: Adaptive population coding in weakly electric fish

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Sensory systems must continuously adapt their coding strategy to efficiently code natural stimuli with time-varying statistics. While adaptation at the single neuron level is relatively well understood, much less is known about adaptation operates at the population level. For example, in the electrosensory system of the weakly electric fish Apteronotus leptorhynchus, a previous study of our group (Huang et al. 2019) has shown that, when presented with a change in stimulus statistics, single neurons will change their response properties to optimally encode the new stimulus, which in turn optimizes the animal's behavioral response. However, as this study was conducted by gathering data from single neurons, it is not known how electrosensory neural populations adapt. Here we investigated how electrosensory neural populations in weakly electric fish adapt to changes in the statistics of natural stimuli. To do so, we performed multiunit recording in the hindbrain region of the fish. Our hypothesis is that neural populations will change not only their tuning but also correlations between their trial-to-trial variabilities (i.e., noise correlations) such as to allow downstream areas to more optimally decode information that is needed to elicit perception and behavior.

1-D-96: The role of synchronous spiking in the encoding of vibrotactile stimuli by low-threshold mechanoreceptors

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Despite its known importance in most other sensory systems, the role of synchrony remains to be explored in somatosensation. Spike synchrony is vital for signal propagation between low-threshold mechanoreceptors (LTMRs) and their postsynaptic targets, but the influence of different tactile stimuli on LTMR spike synchrony remains unclear. In response to a periodic stimulus like vibration, synchronous spiking across neurons relies on the timing of spikes relative to the phase of the stimulus cycle (i.e. precision) and the probability of a spike occurring on each cycle (i.e. reliability). As such, through in vivo extracellular recordings in rodents, we measured the reliability and precision of rapid adapting (RA)- and slow adapting (SA)-LTMR responses to vibrotactile stimuli to infer synchronization of spiking across neurons. Results showed that SA and RA afferents synchronize at different frequency ranges. Interestingly, population synchrony was lost at low and high frequencies due to a loss of spiking precision or reliability, respectively. To explore the mechanisms supporting synchrony loss at each frequency extreme, we developed generalized linear models of LTMRs. Differences in the fitted model parameters demonstrate that a shorter refractory period gives RAs the unique ability to respond to and synchronize at high frequencies. The findings of this study strengthen our understanding of synchrony in somatosensory coding

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and the resulting models allow for efficient exploration of the mechanisms underlying tactile signal processing.

1-D-97: Spinal Phox2a projection neurons relay spared nerve injury-induced neuronal plasticity changes from the spinal cord to the brain

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Peripheral nerve injury elicts plastic changes in spinal nociceptive circuits, resulting in allodynia and the development of chronic neuropathic pain (CNP). Eventually, this state causes maladaptive changes in nociceptive circuits in the brain, frequently leading to increased anxiety and depression comorbidities in CNP patients. Little is known about the precise role of spinal projection neurons in the transmission of CNP-evoked plastic changes from the spinal cord to the brain. We recently characterised a population of spinal dorsal horn projection neurons that express the transcription factor Phox2a, whose spinal cord-specific loss (Phox2aSpC) results in impaired innervation of brain targets and a reduction of nocifensive behaviours that require such connections. To determine the role of this molecularly defined population of projection neurons in CNP, spared nerve injury (SNI) was induced in Phox2aSpC and control mice. The development of mechanical and thermal hypersensitivity, as well as increase in neuronal cFos expression at spinal levels did not differ significantly between these two groups. However, SNI-evoked licking response to cold allodynia was attenuated in Phox2aSpC mice, compared to controls. The analysis of the impact of SNI on neuronal and microglial activity in the parabrachial nucleus and cognitive behaviours in Phox2aSpC mice is pending. Together, our results argue that the normal function of spinal Phox2a projection neurons are required for the development of supraspinal effects of SNI and may constitute a therapeutic target for relief of CNP.

E - Homeostatic and Neuroendocrine Systems

1-E-98: Feeling hungry? The role of fat stores in hypothalamic neurons on energy balance

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Neurons of the hypothalamic arcuate nucleus (ARC) integrate nutritional signals to modulate energy balance. Evidences suggest that the underlying mechanisms involve the release of fatty acids (FA) from intracellular lipid droplets (LD). This model is supported by data from our lab showing that neurons can form and accumulate triglycerides in LD. In addition, our data and single-cell RNAseq studies show that Adipose Triglyceride Lipase (ATGL) is expressed in ARC pro-opiomelanocortin (POMC) neurons that play a crucial role in energy balance. Thus, we propose that ATGL in ARC POMC neurons is involved in energy balance control by regulating LD lipolysis. To test this, we quantified LD and oxidation of FA in hypothalamic neurons (cell lines and primary cultures) treated with oleate, forskolin (ATGL activator in adipose tissues), or Atglistatin (ATGL inhibitor). Also, we generated POMC

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specific ATGL KO mice (Cre-Lox) which were subjected to metabolic phenotyping. Our results show that hypothalamic neurons accumulate LD in response to Atglistatin/oleate, forskolin decreases LDs via ATGL and Atglistatin decreases the oxidation rate of LD-derived FA. Our lipidomics data show that palmitate and oleate are the major FA in neuronal LD. In our mouse model, ATGL KO in POMC neurons does not affect body weight or food intake in chow-fed males. These animals will be subjected to metabolic challenges (high fat diet) to assess the role of ATGL in adaptive metabolic responses. Our data show for the first time that hypothalamic neurons can accumulate LD and that ATGL activates LD lipolysis.

1-E-99: Chronic stress & metabolism in females: evaluating two novel models of female social defeat stress

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Social defeat is a preclinical model to study the effects of chronic psychosocial stress in rodents, as it recapitulates many stress-induced pathologies observed in humans, including metabolic changes. This model, however, is based off male territorial aggression that is not applicable to female rodents. To investigate how females respond to psychosocial stress, we tested two adaptations to the social defeat paradigm to study the effect of chronic stress on metabolism in females. In the first paradigm, fighting females, a female and castrated male CD-1 are cohoused for several days, priming the CD-1 female to display territorial behaviors towards an intruding C57 female mouse. In the second paradigm, non-discriminatory social defeat, we introduced a C57 male and female simultaneously to a CD-1 male mouse. The intruding male provokes territorial aggression towards both the male and female mice. We tested both paradigms for 21-days and gave mice access to chow and a high fat diet, ad lib. Females in the non-discriminatory model displayed changes to hormone levels and metabolism commonly associated with chronic stress. These mice increased their consumption of the standard chow diet, high in carbohydrates, when stressed and had elevated ghrelin and corticosterone levels. Females from the fighting female's paradigm, however, did not display the same markers of chronic stress. Our results highlight discrepancies in the magnitude of stress elicited by each paradigm, with the second paradigm inducing metabolic changes in females commonly observed in males following social defeat.

1-E-100: Periadolescent oxytocin treatment increased neurogenesis in a sex-dependent manner and ameliorated maternal corticosterone effects in adult offspring

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Perinatal depression (PND) affects 15% of mothers and selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for PND. Perinatal SSRI exposure have been controversially linked to increased risk of autism spectrum disorder (ASD) in children. Oxytocin (OT) is under investigation as a treatment for ASD, but OT is a large neuropeptide that has difficulty crossing the blood-brain barrier (BBB). TriozanTM is a nanoformulation that can facilitate OT across the BBB. Here, we hypothesize that using a model of de novo

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postpartum depression, maternal treatments will alter adult offspring social behaviour, neuroinflammation, and neurogenesis in a sex-specific manner and that OT may reverse the effects of maternal treatments. Corticosterone (CORT; 40mg/kg, s.c) was given to dams to model de novo postpartum depression, with or without the SSRI, fluoxetine (FLX; 10mg/kg, s.c.) for 21 days. Offspring were then treated with either OT (0.5 mg/kg), OT+TriozanTM (OT+T; 0.25mg/mL; adjusted to 0.5mg/kg), or vehicle for 10 days prior to adolescence (PD25-34). OT treatment increased neurogenesis only in adult males, regardless of maternal treatment and increased social investigation in both sexes although this depended on maternal CORT. Maternal CORT shifted the IL-6:IL:10 ratio towards proinflammation and increased neurogenesis in both sexes, whereas OT, independent of formulation, reversed these effects. These findings underscore that preadolescent exposure to OT can reverse some of the long-lasting effects of postpartum maternal CORT in adult offspring.

1-E-101: Molecular and behavioural consequences of a striatal bmal1 knockout in mice

Cassandra Goldfarb[1], Konrad Schottner[1], Margo Button[1], Andreas Bergdahl[1], Shimon Amir[1]

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Circadian rhythms, 24-hour oscillations within an organism generated by biological clocks, keep temporal order of molecular, physiological, and behavioral processes with respect to daily changes in the environment, thus enabling systemic homeostasis and proper function of the biological system. A multi-oscillatory network of circadian pacemakers, comprising a central clock in the suprachiasmatic nucleus of the hypothalamus, and peripheral clocks located in other brain regions and tissues throughout the body, sustains tissue-specific rhythms, such as in the striatum. The striatum, a region of the basal ganglia that receives dopaminergic input from the midbrain, controls motor functions and behavioral processes related to mood and reward. Proper function of the striatum is presumably maintained by a mutual interaction of components of the circadian clock and the dopamine signalling pathway. Using a conditional knockout of the core clock gene Bmal1 within medium spiny neurons (MSNs) of the striatum, we assessed the molecular, physiological, and behavioural consequences of striatal clock malfunction. Male and female knockout mice showed deficits in motor coordination and control, but were less affected in mood-related tests. Daily rhythms of gene expression, primarily targeting the circadian clockwork and cell signalling pathways, were also studied, in addition to measurements of mitochondrial respiration in MSNs. Preliminary results indicate changes in molecular and physiological processes in MSNs of knockout animals, that may contribute to the observed behavioural phenotypes.

1-E-102: Divergent electrophysiological and morphological properties of hypothalamic paraventricular nucleus neurons between the common marmoset and the mouse

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The release of stress hormones via the hypothalamic-pituitary-adrenal (HPA) axis is thought to be preserved across mammals. The apex of the HPA axis is formed by neuroendocrine neurons in the paraventricular nucleus of the hypothalamus (PVN) that release corticotropin

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releasing hormone (CRH). While PVN-CRH neurons have been extensively studied in rodents, studies in primates remain scarce. It is possible that the diurnal activity cycle and complex social lives of primates have exposed them to different stressors, and PVN-CRH neurons have evolved new features under evolutionary pressures. Here, we compared PVN-CRH neurons between mice and the common marmoset (Callithrix jacchus), a New World primate that has emerged as a promising model in neuroscience. Using patch clamp electrophysiology in acute brain slices, combined with post-hoc morphology reconstruction and immunohistochemistry, we characterized marmoset PVN neurons and compared them to their mouse counterparts. Marmoset PVN-CRH neurons showed stereotyped electrophysiological features well-established in rodents and were distinct from other PVN neuron-types. However, marmoset PVN-CRH neurons exhibited substantially larger sag-current and shifted membrane resonance due to hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. Further, morphological analysis revealed that marmoset PVN-CRH neurons exhibit more dendritic spines compared to mice. These distinct features of marmoset PVN-CRH neurons may reflect fundamental differences in synaptic integration adaptive for the lifestyle and stressors of primates.

1-E-103: Effects of short-term glucocorticoid exposure on hippocampal neuronal structure and signaling pathways in female rats

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[1]University of Guelph

Gonadal and adrenal steroids play a fundamental homeostatic role in the brain, maintaining the hippocampal-neocortical circuitry, which is important for learning, memory and mood regulation. Previous work in our laboratory has demonstrated changes in hippocampal dendritic morphology in males, but not females, following gonadectomy. Acute glucocorticoid exposure in male rats mirrored this effect, suggesting that surgical stress results in pruning of the hippocampal CA3 apical dendrites. The consequences of short-term stress in females have not been as well characterized. We investigated the effects of acute glucocorticoid exposure in cycling female Sprague-Dawley rats by treatment with the synthetic glucocorticoid Dexamethasone (DEX) in the drinking water for 16h, at a dose designed to mimic the effects of acute stress. The animals were sacrificed during proestrus, when circulating estradiol (E) levels are at a maximum. DEX significantly decreased apical dendritic spine density in CA1 and CA3 at 1 and 5 days following treatment. The dendritic branching patterns and length were significantly increased in CA3 dendrites at 1 day. These effects were accompanied by increased phosphorylation of the MAPK signaling proteins, ERK and JNK, as well as increased levels of the ERK-specific phosphatase, DUSP6. These results indicate differences between the sexes in the effects of brief glucocorticoid exposure on hippocampal neuronal structure, possibly as a result of E-induced increases in the activity of the MAP kinase pathways involved in dendrite growth, in females but not in males.

F - Cognition and Behavior

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1-F-104: Mesencephalic transcranial ultrasound in patients with type 1 bipolar mood disorder showed Raphe nucleus hypoechogenicity and 3rd ventricle diameter elevation in comparison with the control group.

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Advancements in Ultrasound techniques such as Transcranial ultrasound or TCS, led us to detect Structural disturbances such as echogenicity changes of the brain raphe, as well as the assessment of the diameter of the third ventricle, in many psychiatric disorders such as type 2 bipolar mood disorders, major unipolar depression, psychosis as well as organic - neurodegenerative disorders, etc. Various similar studies indicated that tissue degeneration involved in functional neurons of the serotonergic and dopaminergic systems in the limbic system, brainstem networks. There is a lack of consensus among researchers in previous studies on type 1 bipolar mood disorder, which guided us to conduct our research. In this observational case-control study,80 samples, including 27 patients with confirmed nonpsychotic type 1 bipolar disorder, hospitalized at the psychiatric ward and 53 subjects in the correlated healthy control group, were randomly selected. Respectively Transcranial ultrasound or TCS was performed in order to find out the disturbances of brain stem Raphe Echogenicity and also determining the 3rd ventricular diameter. Considering the disappearance of the structure as abnormal structure, 9 (33.3%) of patients and in comparison with the control group, 5 subjects (9%) showed a significant depletion in RN echogenicity. Also, 7 patients and 3 controlled subjects showed a significant third ventricular diameter elevation. In this study, we concluded that the echogenicity of brain stem Raphe was significantly reduced (p-value: 0.008) and the Diameter of the third ventricular significantly increased (p-value: 0.01) among the nonpsychotic type 1 bipolar patients comparing to the healthy correlated control group.

1-F-105: Early life stress modifies fear-induced glutamate release and parvalbumin interneuron maturation in the medial prefrontal cortex of juvenile rats.

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Early life stress (ELS) increases vulnerability to psychiatric disorders associated with emotional dysregulation. The corticolimbic circuit is important for fear conditioning and is highly sensitive to environmental stressors during early 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 glutamatergic tone in the infralimbic (IL) and prelimbic (PL) medial prefrontal cortex (mPFC) during the juvenile period, a time of peak GABAergic inhibitory tone. We measured glutamate concentrations during fear conditioning using in vivo microdialysis in behaving juvenile (PND28-32) rats. We report that while LB conditions enhanced behavioral fear expression in juvenile males but not females, fear-induced glutamate response in the right PL, but not IL mPFC was diminished in male LB offspring compared to controls. To estimate ELS effects on parvalbumin (PV) interneurons and their maturational state, we determined PV neuronal density and the proportion of PV neurons expressing perineuronal nets (PNNs). Formation of PNNs is associated with the

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closure of periods of plasticity and stabilizes GABAergic output of PV neurons. Total PV population in PL mPFC was not altered by ELS in male juveniles, but fewer PV neurons expressed PNNs. These results suggest that ELS differentially affects glutamatergic neurotransmission in the PL and IL mPFC during fear conditioning in juveniles and might delay the maturation of PNNs around PV interneurons and maintain a higher inhibitory tone in the PL mPFC.

1-F-106: Long-term behavioural effects of concurrent alcohol and nicotine vapour exposure during adolescence in adult male and female Sprague-Dawley rats

Jessica Ruffolo[1], Jude Frie[1], Jibran Khokhar[1]

[1]University of Guelph

AIM: The co-occurrence of electronic cigarette (e-cigarette) use and alcohol consumption during adolescence is frequent and well documented. However, little is known about their long-term effects on subsequent behavioural outcomes in adulthood. This highlights the importance in elucidating the consequences of concurrent alcohol and nicotine vapour exposure during such a vulnerable developmental period. METHODS: Male and female Sprague-Dawley rats (n=8-11/group/sex) received either nicotine (JUUL 5% nicotine) or vehicle (30:70 propylene glycol to glycerol) vapour daily from post-natal day (PND) 30-46 and had continuous voluntary access to ethanol (10% v/v) or water in adolescence. Upon adulthood, rats began Pavlovian conditioned approach (PCA) testing, where they learned that a lever presentation predicted a non-contingent reward delivery. Preference toward the reward receptacle indicated goal-tracking behaviour. Preference toward the lever indicated sign-tracking behaviour, demonstrating that the lever had acquired incentive salience. RESULTS: Males co-exposed to alcohol and nicotine vapour during adolescence exhibited significantly higher levels of sign-tracking behaviours in adulthood compared to male controls. No significant effects were observed in females. CONCLUSION: Our results support the notion that adolescent co-exposure to alcohol and nicotine vapour produces marked changes in behaviours in adulthood. Delineating the long-term ramifications of alcohol and nicotine vapour will be vital for understanding their interactions when concurrently used in adolescence.

1-F-108: Age-related declines in context memory and medial temporal lobe volume

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Age-related decline in episodic memory for contextual details (context memory) arises in early midlife, and is associated with altered brain activity in the medial temporal lobes (MTL). Previous work has observed that cognitive decline and structural integrity of the hippocampus appear to be tightly coupled across the adult lifespan, and that MTL structure appears to influence memory performance. However, it remains unclear if age-related atrophy within the MTL mediates age-related decline in context memory. Thus, the goal of this project was to investigate the intersection between age-related declines in MTL volume and context memory. We tested 132 participants across the adult lifespan on spatial and temporal context memory tasks. We employed a semi-automated segmentation protocol to segment the perirhinal, entorhinal and parahippocampal cortices, and the anterior and

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posterior segments of the hippocampus. We then computed multiple mediator models to investigate how MTL volumes mediated age-related declines in context memory. These analyses revealed that age-related atrophy of the posterior hippocampus, but not any other MTL structure, fully mediated the association between age and spatial context memory performance (βab = -0.17, 95% CI [-0.28, -0.07]). Further, we are currently investigating investigating structure-function interactions to assess whether there is a relationship between age-related declines in MTL volume and task-related functional activation in aging.

1-F-109: The segregation of task-based EEG networks into functionally specialized systems is reduced in those with hyperactive traits

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Although attention-deficit/hyperactivity disorder (ADHD) is associated with the atypical development of large-scale brain networks, network organization in those with different ADHD-traits (inattention/hyperactivity) is not well understood. Here, we examine the relationship between ADHD traits and EEG functional networks during an attentional control task. To do so, 128-channel EEG was recorded while 62 non-clinical participants (ages 18-24) underwent a Go/No-Go task. Networks were created using EEG sensors as nodes and across-trial phase-lag index values as edges (10% threshold, binarized). Using cross-validated LASSO regression, we examined whether dynamic graph-theory metrics of integration, segregation and modularity predict inattention and/or hyperactivity. In the gamma-band (30-90Hz), and no other frequency bands, a three feature model accounted for a substantial amount of variance in hyperactivity (R2 = .28). This showed that throughout processing (0-500ms, 2ms intervals), networks of those with low hyperactivity: (1) have nodes which tend to remain in the same module (r = -.44, p = .0004), (2) consistently share connections with the same neighbours (r = -.34, p = .007), and (3) take more time to transfer information globally (r = .36, p = .004; all powers > .85). Thus, the well-reported developmental process whereby task-specific systems of brain regions become increasingly specialized might be protracted in the ADHD Hyperactive-Impulsive subtype. Understanding which developmental processes might be altered in ADHD has implications for diagnosis and intervention.

1-F-110: Intravenous Reelin has fast-acting antidepressant-like effects evaluated in the repeated corticosterone-paradigm of chronic stress

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Depression is a devastating mental illness and current antidepressants have a slow therapeutic onset and only work in some patients. Chronic corticosterone (CORT) treatment produces a depressive-like phenotype in rats that is associated with deficient hippocampal neuroplasticity and altered serotonin transporter (SERT) membrane protein clustering (MPC) in blood lymphocytes. We recently found that Reelin, an extracellular matrix neuromodulator, rapidly rescues CORT-induced depressive behavior when infused intrahippocampally. As Reelin is also present in blood we examined if intravenous Reelin injections also have antidepressant-like effects. Rats received daily vehicle or CORT injections for 21 days along

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with vehicle or 3µg of Reelin given every 10 days, or a single injection (0.5, 1, 3, 5, 7 or 9µg) on day 21. Rats were then subjected to forced swim (FST) and object-recognition memory tests followed by postmortem analyses of hippocampal Reelin, GABAAβ2/3, GluA1 and GluN2B expression, as well as SERT MPC parameters. Repeated intravenous Reelin attenuated CORT-induced FST-immobility, restored cognitive ability, and normalized SGZ-Reelin-positive cell number and the expression of GABAAβ2/3, GluA1 and GluN2B receptors. A single Reelin injection at the end of CORT treatment partially rescued behavioral deficits, Reelin-positive cell number, and the size of SERT clusters on lymphocytes, and fully recovered GluA1 expression. These findings show that intravenous Reelin has fast-acting antidepressant-like effects associated with the restoration of hippocampal neurochemical deficits and SERT MPC on lymphocytes. Although additional mechanistic and pharmacokinetic studies are necessary, our data open the possibility to develop Reelin peptides with putative antidepressant activity.

1-F-111: Activation of muscarinic cholinergic receptors is critical for the destabilization of otherwise-resistant spatial memories

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Following exposure to reminder cues associated with a previous learning experience, consolidated memories can become destabilized. This renders them labile, where they are vulnerable to weakening or other modifications. However, stronger or older memories can resist destabilization, only becoming labile when exposed to novelty during memory reactivation. Destabilized memories must then be reconsolidated in order for the information to persist within long-term memory. Using rats, we have previously shown that both object and spatial memory destabilization requires acetylcholine acting at muscarinic cholinergic receptors (mAChRs) within perirhinal cortex and the dorsal hippocampus, respectively. Here, we utilized the object location task to demonstrate that 1) NMDA receptor antagonism with MK-801 (0.1 mg/kg, ip) prevents spatial memory reconsolidation in male mice, 2) strongly encoded object location memories resist destabilization, but exposure to novelty during reactivation renders them labile and vulnerable to weakening, 3) non-specific mAChR antagonism with scopolamine (0.3 mg/kg, ip) prevents both standard and novelty-induced destabilization of object location memories. These findings provide converging evidence to support the idea that cholinergic activity at mAChRs is critical for the destabilization of otherwise-resistant memories. In addition, this research enhances our understanding of the dynamics of long-term memory storage and suggests implications for the understanding and treatment of disorders characterized by inflexible memories, such as Alzheimer's' Disease and PTSD.

1-F-112: Lactate dehydrogenase influences long-term courtship memory in aged Drosophila melanogaster

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Maintaining energy levels in the brain is crucial for both health and cognitive function. Aging tends to negatively impact cognition, highlighting the importance of maintaining the metabolic demands of the aging brain. Studies have shown that lactate generated by glial

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glycolysis is shuttled to neurons to enable sufficient fuel for oxidative metabolism required for long-term memory (LTM) formation. However, it is unknown if glial/neuronal metabolic coupling declines or is dysregulated with aging. This study uses the genetically tractable short-lived invertebrate model organism Drosophila melanogaster (fruit flies) to shed light on this question. Previous studies have shown shuttling of lactate from glia to neurons in the brain of flies, but whether this metabolic coupling has any impact on memory or exhibit changes with age is unknown. Flies were genetically manipulated to either overexpress or repress expression of lactate dehydrogenase (dLdh), the rate-limiting enzyme interconverting pyruvate and lactate, within glia or neurons. Surprisingly, both increased and repressed expression of neuronal dLdh resulted in reduced lifespan, whereas in glia, only upregulated dLdh reduced lifespan. LTM, measured by courtship conditioning, was diminished exclusively in aged flies with either neuronal dLdh up- or downregulation and with glial dLdh downregulation. Flies with neuronal dLdh upregulation exhibited and accelerated age-related decline in climbing ability, indicating a more rapid deterioration in general health. Decreased LTM in aged flies due to altered dLdh indicates that neuron-glia lactate shuttling may play a role in invertebrate aging and memory.

1-F-113: Effect of social context on subsequent pain experience and neural activation in mice

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Social animals can pick up signals from group members that indicate changes in the environment, including threat or potential for injury. Signals from group members indicating a potential for pain or injury likely range across modalities of perception, including visual cues like paw licking, vocalizations, and olfactory cues. Interestingly, the social context plays a significant role in enhancing pain behavior. Research in mice has shown that when together, familiar mice express more pain than when alone, and observer mice develop sensitivity to painful stimuli after interacting with cagemates in pain. Yet the neural mechanisms that drive the enhancement of pain due to social stimuli are unknown. Our aim was to develop a short paradigm where mice express overt cues of pain, and then begin to understand the mechanisms underlying the enhanced pain behavior in the uninjured partner. We show behavioral pharmacology and immunohistochemistry data using our social paradigm.

1-F-114: Developmental onset distinguishes three types of spontaneous recognition memory in mice

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Recognition memory explores the what, where and when components of episodic memory. Using the animal's natural tendency towards novelty, spontaneous recognition memory tasks allow for the study of the neural underpinnings of learning and memory. Spontaneous recognition memory deficits are common in rodent models of neurodevelopmental disorders, and yet very little is known about the expression of spontaneous recognition memory in young rodents. To address this, we sought to establish the ontogeny of three types of

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spontaneous recognition memory in mice: object location (OL), novel object recognition (NOR) and temporal order recognition (TOR). In OL, animals must recognize a change in location of a familiar object (where). In NOR, they are presented with a novel object (what). In TOR, animals must distinguish between two objects based on how recently they interacted with them (when). We found that C57/129J mice first displayed recognition memory for OL, at postnatal day (P)21, followed by NOR expression at P25, and lastly expressed TOR memory at P28. No correlation was found between memory performance and total object exploration for any age or task, suggesting that this time of onset is not a result of age-dependent changes in object exploration time. Determining the onset of spontaneous recognition memory tasks in mice is an important first step towards a better understanding of the maturation of episodic memory, and will provide the necessary foundation for the use of these tasks in clinically relevant time points in animal models of disease.

1-F-115: Effects of androgens on behavioural flexibility in male rats

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Behavioural flexibility, the ability to adapt behaviour in response to environmental changes, is regulated by the mesocorticolimbic system. In strategy set shifting, subjects initially learn to use one rule to receive a reward (e.g. select the lever denoted by a cue light, known as cue rule), but then must switch to a new rule (e.g. select the left/right lever, known as response rule). Treatment with androgens, such as testosterone, impairs set shifting. Moreover, we previously showed that decreasing androgens with an androgen synthesis inhibitor (abiraterone) facilitates behavioural flexibility (shift from cue rule to response rule). The effect size of abiraterone treatment, however, was small. To increase the effect size of abiraterone, we modified the set shifting task to be more difficult. Here, we manipulated the order of the shift, the minimum number of learning trials during the initial discrimination, and the presence of reminder trials immediately prior to the set shift. Rats were assigned to one of six different set shifting tasks, which required them to perform either the cue-response shift or response-cue shift with variable numbers of minimum learning trials and with or without reminder trials. Rats performing the response-cue shift made significantly more errors to criterion compared to rats performing the cue-response shift. There were no effects of minimum number of learning trials or reminder trials. Ongoing work will examine the effects of abiraterone on the two types of shift.

1-F-116: Novelty detection in two avian species

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Our understanding of the avian hippocampal formation (HF) may be furthered by studying spatial behaviours that are less species-specific, as this permits direct comparisons between avian families, and potentially across classes. Towards this goal, we adapted a y-maze test from mammalian studies. In the easiest variation of the task, birds explore a y-maze for 5 minutes with one arm blocked. After a 1 minute delay, the subject is placed back into the maze with all arms open at test. In the hardest variation, birds explore two identical y-mazes with different arms blocked in two different rooms with unique extra-maze cues. Birds then explore both mazes with all arms open. Both Japanese quail (Coturnix japonica) and Silver

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King pigeons (Columba livia) show preference for the novel arm in a single y-maze, but only pigeons differentiate between the two contexts. These data show that reaction to novelty can be utilized across a number of avian species as the basis for testing spatial cognition. Studies of this nature may provide evidence that a number of tasks previously used exclusively in mammals may be adapted for birds.

1-F-118: Ultrasonic vocalization analysis as a novel metric to assess home cage welfare in rats

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Laboratory rodent housing conditions vary significantly across laboratories and facilities. Variation in housing is implicated in animal stress leading to study variability and subsequently the ability to replicate experimental findings. Optimization and standardization of animal housing conditions are necessary to improve animal welfare and data consistency, thereby reducing the number of animals necessary to detect treatment effects. While interest in environmental enrichment is increasing, many studies do not examine the behavior of animals within the home cage, neglecting important aspects of enrichment. To determine the impact of increased vertical home cage area on animal welfare, double-decker cages (enriched), which allow animals to rear (stand on hind legs), were compared to single-level cages (standard), which impede the ability to rear. Home cage welfare was assessed by analyzing ultrasonic vocalizations, fecal corticosterone, rearing and agonistic behavior. Ultrasonic vocalization content was further explored by analyses of call type as defined by a 14 call-type schematic. Contrary to our expectations, rats housed in enriched cages spent more time fighting, produced less 50 kHz calls and had higher levels of fecal corticosterone. Standard caged animals attempted to rear more, but reared for a shorter amount of time due to the height limitation imposed by standard cages. Standard cages restrict some naturalistic behaviors such as rearing, but reduce agonistic behavior which may be attributable to their single-tier organization. Increased home cage height is beneficial, as it permits rats to engage in normal ethological behavior. However, the inclusion of a continuous "upper deck" appears to increase dominance/aggressivebehavior among cage mates.

1-F-119: Analysis of memory modulation by an avoidance cue: role of noradrenaline and dopamine

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Exposure to emotional conditioned stimuli (CS) enhance memory consolidation, a process of memory stabilization that involves noradrenergic (NA) activity. However, these CSs not only generate conditioned fear, but they also serve as predictors that a US is about to occur, and this function appears dependent on mesolimbic dopamine (DA) activity. Therefore, this study explored whether both NA and DA are involved in the memory enhancing action of an avoidance CS. Male Sprague-Dawley rats trained on a signalled active avoidance task (8 days; 30 trials/day; 0.8 mA) were exposed to the avoidance CS immediately following the sample phase of the Object Recognition task. Different groups were pre-treated with the ß-noradrenergic receptor antagonist propranolol (0, 10, 20 mg/kg) or the DA D2 antagonist pimozide (0, 0.2, 0.6 mg/kg). All groups were tested for object memory 72h later, in drug free

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conditions. It was found that immediate post-sample exposure to the avoidance CS in the absence of shock enhanced object memory, and that this effect was dose-dependently blocked by both propranolol and pimozide. Overall, these results indicate that the memory-enhancing effect of an avoidance CS requires both NA and DA neurotransmission.

1-F-120: Ghrelin, cannabinoids, and motivation: increased food motivation on progressive ratio conditioning through MAGL/FAAH inhibition in a rat model

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Ghrelin stimulates food intake in part by increasing motivated behaviours through its receptor (GHSR) in the ventral tegmental area (VTA). Recent data suggest that ghrelin may interact with the endocannabinoid system in the VTA to produce these effects. It is hypothesized that ghrelin may influence this system by stimulating the release of endocannabinoids from dopamine cells through its action on the GHSR, via increased synthesis and accumulation of membrane bound cannabinoid enzymes. Previous data from our lab show peripheral ghrelin injections increases 2AG in the VTA. To examine if ghrelin alters the expression of enzymes that synthesize or degrade 2AG, male and female WT and GHSR KO rats were given an i.p. injection of saline or ghrelin (1 mg/kg). Western blot analysis showed lower VTA MAGL of GHSR KO rats compared to WT. Ghrelin also increased MAGL in the VTA of WT females. Next, we examined the behavioural effects of blocking MAGL/FAAH on ghrelin induced reward seeking behaviour using an exponential operant conditioning paradigm. Rats received a unilateral VTA infusion of endocannabinoid degrading enzymes inhibitor (MJN110/PF-00457845) cocktail (5µg and 3µg/0.5µl, respectively), followed by an infusion of ghrelin (0.5µg/0.5µl). Pre-treatment with the inhibitor cocktail enhanced the effects of ghrelin in the VTA. This suggests that ghrelin may act on the VTA to increase reward seeking behaviours via 2AG regulating mechanisms. Moreover, our data suggest that ghrelin stimulates the production of MAGL as a feedforward regulatory process to regulate 2AG. Funded by NSERC.

1-F-121: Systemic M1 muscarinic acetylcholine receptor activation can restore aging-related object memory updating deficits in mice

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Memory reactivation (RA) can facilitate trace destabilization, enabling memory updating. Some memories, however, are resistant to modification. Specifically, elderly individuals display deficits in declarative memory updating. There is currently no treatment to target this cognitive impairment, likely because factors mediating RA-based memory updating remain unclear. We propose that cholinergic signalling supports RA-based memory changes. Recent findings in our lab suggest that M1-muscarinic acetylcholine receptor (mAChR) signalling within perirhinal cortex supports object memory destabilization and RA-based updating. Correspondingly, aging research indicates a decline in cholinergic transmission across the lifespan. Therefore, we hypothesize that age-related cholinergic system dysfunction underlies memory updating deficits in elderly individuals. To test this, we used a post-RA object memory modification (PROMM) task--where a reactivated object memory is updated with new contextual information--to assess object memory updating in 3-, 6-, and 12-month-

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old male mice. 3-month-old mice showed intact PROMM task performance, 6-month-old mice showed a mild impairment, while 12-month-old mice were severely impaired. Subsequently, we administered the M1-selective agonist CDD-0102A prior to object memory RA in the PROMM task in the 12-month-old male mice; remarkably, pre-RA systemic M1-mAChR agonism enhanced PROMM task performance. These results therefore suggest a promising neural target for promoting the modification of inflexible memories in aged populations.

1-F-122: The hippocampus promotes long-term memory formation by preventing sensory interference

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Damage to the medial temporal lobe, notably the hippocampus, often leads to anterograde amnesia for declarative memories, but it remains unresolved how this deficit arises. Active decay theory proposes that the hippocampus is recruited in long-term memory formation to provide a "protective index" to shield extra-hippocampal content representations from disruption by interference from ongoing sensory stimulation. Thus, when hippocampal functioning is impaired, natural sensory experience after learning will lead to states of catastrophic interference in these regions, ultimately manifesting as amnesia. To test this hypothesis, we used an object recognition task in rats as a model for human declarative memories, as expression of long-term object memory requires the perirhinal cortex, not the hippocampus. We found that inactivating the hippocampus prior to object learning with intrahippocampal injections of GABAA and -B agonists (muscimol+baclofen) impaired object recognition tested 24h after learning. This deficit was absent when we reduced sensory stimulation after learning. Next, we blocked memory formation in the hippocampus by infusing the NMDA receptor antagonist AP5 prior and after object exposure. Here, preventing hippocampal memory formation before, but not after object learning led to amnesia for objects 24h later, which was absent when we reduced sensory stimulation after learning. Our findings suggest that the hippocampus protects object representations in other brain regions from sensory interference after learning, thereby promoting their stabilization.

1-F-123: Knocking down glycogen synthase kinase-3 beta (GSK3b) in cortical neurons affects the mouse electrocorticogram across vigilance states

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Current hypotheses propose that sleep/wake regulation depends on both the circadian clock and a homeostatic process. The glycogen synthase kinase-3 beta (GSK3b) regulates the activity of key circadian transcription factors (e.g., BMAL1, CLOCK). GSK3b is also involved in long-term depression and metaplasticity. Moreover, FXR1, a GSK3b substrate, has recently been shown to affect both cell-autonomous homeostatic plasticity and system-level response to sleep loss in a GSK3b-dependent manner. This project thus aims to investigate a potential role of GSK3b in circadian and homeostatic sleep/wake regulation by verifying how its knockdown (KD) in cortical neurons impacts vigilance states under normal (baseline: BL) and sleep-deprived (SD) conditions. A neuron-specific KD of Gsk3b was achieved in adult male mice via dual adeno-associated virus delivery of a CRISPR/Cas9 system. Cortical

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viral injections and electrocorticography (ECoG)/electromyography (EMG) electrodes implantation surgeries were done simultaneously 3 weeks prior to ECoG/EMG recording, which comprises 24 h of BL, 6 h of SD, and 18 h of recovery. Analyses notably include vigilance state duration/distribution and ECoG spectral activity. Gsk3b KD did not affect the time spent in wakefulness and sleep states nor the alternation between states. However, the KD of Gsk3b in the motor cortex decreased gamma (30-50 Hz) activity during wakefulness and alpha (8-10 Hz) activity during slow-wave sleep (SWS). Moreover, a SD-induced increase in beta/gamma (20-50 Hz) activity during SWS was found in the visual cortex only under Gsk3b KD. These results support a role for GSK3b in the regulation of ECoG activity during wakefulness and sleep, and bring a deeper insight on molecular mechanisms controlling vigilance state quality.

1-F-124: Investigating the mechanisms of neurogenesis-based forgetting using zebrafish

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Rather than strive for perfect memory, our brains have evolved a different strategy: remember some and forget most. Neurogenesis within the hippocampus is one of the fundamental neurobiological processes of forgetting in the mammalian brain. Upregulation of cell proliferation in neurogenic niches responsible for memory encoding and storage results in the disruption of existing memory circuits and thus forgetting. However, the mechanisms of neurogenesis-induced forgetting remain obscure. Zebrafish exhibit robust levels of post-embryonic neurogenesis and are amenable to advanced optical approaches. These attributes facilitate the investigation of neurogenesis and its impact on neural circuits involved in memory. The teleost dorsolateral pallium (Dl), homologous to mammalian hippocampus, is involved in memory storage and shows an increase in neurogenesis after exercise in larval zebrafish. We hypothesize upregulation of neurogenesis within Dl will cause zebrafish to forget the association between a visual cue paired with an aversive conditioned stimulus. To do so, we developed an exercise assay where increased water circulation induces fish to swim against a current. We found that increased levels of swimming resulted in a significant upregulation of cell proliferation in the forebrain after 14 days. To examine the integration of newly born neurons into mature circuits, we developed a fate mapping approach to temporally tag cycling radial glia populations and their progeny. Next steps for this research involve combining our aversive learning paradigm with exercise to determine if increased levels of neurogenesis lead to reduced memory recall (forgetting).

1-F-125: Altered activity in functional brain networks involved in lexical decision in bipolar disorder

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Bipolar disorder (BD) is associated with language disturbances such as speech pressure and poverty of speech. However, little is known about the neurophysiology underlying language

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deficits in BD. In a previous study, we extracted three functional brain networks (i.e., a linguistic processing network - LPN, default mode network - DMN, and motor response network - RESP) involved in the lexical decision (LD) task by manipulating the "word-likeness" of LD stimuli combined with a multivariate functional connectivity analysis in healthy adults. Here, we applied the same techniques to determine if these three networks could be extracted in people with BD. The BD patients (n = 25) were also compared to controls (n = 21) to assess possible difficulties in LD task performance and abnormal activity in the three functional networks in BD. There were no differences between BD patients and controls in their accuracy or reaction times in the LD task. We replicated our previous work in healthy subjects as we were able to separate the LPN from the DMN and RESP. LPN activity did not differ between the groups, which is in line with the lack of significant differences in LD task performance between BD and control. BD was associated with sustained activity in the RESP, which involves activations in left-dominant pre- and post-central gyri and juxtapositional lobule cortex, as well as bilateral activations in superior and inferior lateral occipital cortex, superior parietal lobule, and occipital fusiform gyrus. Impairment in RESP may be observed in any task and could potentially be a biomarker for BD.

1-F-126: Conditioned effects of a ketamine-paired context: implications for its antidepressant mechanism

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It has been proposed that a context paired with ketamine (KET) can elicit an antidepressant response through principles of Pavlovian conditioning. This raises the question as to whether this conditioned antidepressant response is unique to KET, or whether it can be generalized to other antidepressant drugs with known pharmacological mechanisms like the serotonin reuptake inhibitor, escitalopram (ESC), or the norepinephrine-dopamine reuptake inhibitor, bupropion (BUP). Thus, the current study investigated whether a context paired with KET, ESC, or BUP could influence the immobility response to forced swimming stress (FSS; 10 mins/session, 3 sessions total), which is a preclinical tool used to assess the antidepressant efficacy of drugs. To do this, male Sprague-Dawley rats were injected with 0.9% saline (w/v; SAL) and placed in a vehicle-paired context (CS-) and injected with SAL, KET (10 or 20 mg/kg, IP), ESC (10 mg/kg, IP), or BUP (10 mg/kg, IP) and placed in a drug-paired context (CS+) on alternating days (10 days total, 5 pairings each in the CS- and CS+). One week later, rats were exposed to 3 sessions of FSS over 3 consecutive days (FSS1-3; exposure to CS- and CS+ prior to FSS2 and FSS3, respectively). Exposure to a KET-paired context prior to FSS3 significantly reduced immobility without affecting general locomotor activity in comparison to contexts paired with SAL or BUP, but not ESC. These findings support the notion that a KET-paired context elicits a conditioned antidepressant response, and that this response may partially involve serotonergic mechanisms.

1-F-127: The traditional Chinese medicine component Rhynchophylline modifies sleep and the brain spatial transcriptome in mice

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Ancient medicine drugs containing the alkaloid rhynchophylline (RHY) increase sleep duration and quality in humans. Although treatment with RHY alone has not been tested in humans, rodent studies suggest that it modulates cellular pathways involved in sleep/wake regulation by targeting ion channels and kinases. Interestingly, RHY can inhibit EphA4, and EphA4-/- mice have sleep alterations. We thus studied effects of RHY on sleep and related molecular mechanisms. The electrocorticogram was recorded in male and female mice receiving 50 or 100 mg/kg of RHY (or saline) at light onset and 1h before light offset. Sleep architecture and spectral activity were examined. Additional groups had their brains sampled 3h after each injection to assess changes in the transcriptome with a high spatial resolution. In both sexes, RHY decreases wake and increases NREM sleep during the dark period, and reduces REM sleep during the light period. Moreover, RHY shortens individual bouts of wake and NREM sleep. RHY also enhances activity in low frequencies in wake and modifies the time-course of NREM sleep delta and sigma activity. Preliminary results in females suggest that Rhy affects the expression of genes such as Sgk1 similarly at the beginning of the light and dark periods, while its impact on mitochondrial genes and genes expressed in the hypothalamus appears time-dependent. RHY modifies sleep in manners similar to EphA4-/- mice, but additional effects may suggest EphA4-independent mechanisms. The transcriptomic approach will help defining how RHY impacts wake/sleep regulatory circuits.

1-F-128: Sex-specific effects of voluntary exercise on behavior and the microbiota-gut-brain axis

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Physical exercise has been positioned as a promising strategy to prevent and/or alleviate anxiety and depression but the mechanisms underlying its effects have yet to be determined. This study examined, in mice, the effects of voluntary exercise on depressive- and anxiety-like behaviors. The gut microbiota and markers of intestinal and brain inflammation and permeability were also examined. Male and female C57BL/6 mice were given voluntary home-cage access to running wheels (VRW) for 3 weeks or were left without access to wheels. Behavior was then examined in the elevated plus-maze, open field, tail suspension, and splash tests. Gene expression of pro-inflammatory cytokines, microglia-activation related genes, and tight junction proteins was determined in the jejunum and hippocampus and microbiota composition and function in cecum contents was analyzed through 16S rRNA sequencing and PICRUSt. VWR reduced anxiety-like behavior in males but not females. Higher VWR levels correlated with reduced depressive-like behavior in females only. VWR changed cecal microbial composition, jejunal expression of tight junction proteins, and hippocampal expression of microglia-activation related genes, in a sex-specific manner. These findings support the view that voluntary exercise is beneficial for mental health and that its effects on behavior could be, at least in part, mediated by the microbiota-gut-brain axis. They also suggest that the development of exercise interventions for mental health should consider both sex and exercise dose to optimize efficacy.

1-F-129: Correction of mTORC1-mediated 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. In particular, the mammalian target of rapamycin complex 1 (mTORC1) pathway plays a key role in regulating protein synthesis. Not surprisingly, the mTORC1 signaling has received considerable attention in recent AD research. However, results from such studies remain controversial. In this work, we analyzed the mTORC1 signaling proteins in hippocampi from mice infused intracerebroventricular (i.c.v.) with amyloid-β oligomers (AβO), the major neurotoxins in AD. We found a decrease in the levels of mTORC1 proteins in mice, 7 days after AβO infusion. Further, we tested whether enhancing mRNA translation could rescue defective translation and memory in mouse models of AD. Results show that haploinsufficiency for the translational repressors' eukaryotic initiation factor 4E binding protein 2 (4E-BP2) or Fragile X mental retardation protein (FMRP) prevented the inhibition of brain protein synthesis and memory impairment induced by AβO. These findings establish that targeting mRNA translation initiation corrects translational and memory deficits in AD models, and suggests a potential target to combat cognitive decline in AD.

1-F-130: Assessing the importance of acetylcholine signaling in perirhinal cortex for object memory destabilization using DREADDs in male and female mice.

Cassidy Wideman[1], Jackie Zakaria[1], Jayson Capistrano[1], Kristen Jardine[1], Boyer Winters[1]

[1]University of Guelph

The content of long-term memory is neither fixed nor permanent. Reminder cues can destabilize consolidated memories, rendering them amenable to change before being reconsolidated. Reactivation-induced memory destabilization is thought to reflect a mechanism through which long-term memories can be adaptively maintained over time and has been studied for its therapeutic potential for treating conditions associated with maladaptive memories. However, not all memories destabilize following reactivation. Characteristics of a memory, such as its age or strength, impose boundaries on destabilization. Previously, we demonstrated that presentation of salient novel information at the time of reactivation can readily destabilize resistant object memories in rats. Given its role in cognitive processes involved in attention and new learning, in the current study we hypothesized that acetylcholine (ACh) released in response to novelty at the time of reactivation is necessary to destabilize resistant object memories. Using designer receptors exclusively activated by designer drugs (DREADDs), we found that inhibiting ACh release in perirhinal cortex, a brain region critical for object memory, at the time of reactivation in male and female mice prevents object memory destabilization and the ability to overcome boundary conditions. This research therefore advances our understanding of the neurobiological mechanisms involved in dynamic long-term memory storage and highlights the importance of considering reactivation conditions required to successfully destabilize resistant memories.

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1-F-131: Deletion of the chloride transporter NKCC1 increases hippocampal radial glia-like stem cell pool and impairs flexible learning and memory performance in adult mice

Mahmoud Dahab[1], Edith Goeller[1], Kassandra Reiche[1], Madlen Guenther[1], Leopold Wohlsperger[1], Tom Flossmann[1], Iris Schäffner[2], Christian Schmeer[1], Christian Huebner[1], Otto Witte[1], Knut Holthoff[1], Dieter Chichung Lie[3], Silke Keiner[1]

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During aging in adult mice, spatial memory and cognition decline, leading to navigation problems. This takes place mainly due to the loss of granular neurons and the decrease in the number of radial glia-like cells (RGLs), which generate them. The neurotransmitter GABA is an important intrinsic regulator of adult neurogenesis. The mode of GABA action depends on the intracellular chloride level, which is determined by the differential expression of chloride transporters NKCC1 and KCC2. NKCC1 is predominantly expressed in neural precursor cells and drives cellular Cl- influx. The role of these transporters in RGLs activity of the dentate gyrus remains unknown. In our study, we used a transgenic mouse model (NestinCreERT2/NKCC1fl/fl/tdtomato mice) to specifically delete the NKCC1 transporter in nestin+RGLs. During aging, NKCC1 knockout (NKCC1ko) mice showed a significant increase of the RGLs neural stem cell population in the hippocampal dentate gyrus. To assess changes in learning and memory, we used a modified version of the Morris water maze, which includes a re-learning paradigm. In contrast to the control animals, NKCC1ko mice showed higher latencies to find the platform. In addition, hippocampus-dependent strategies were also highly reduced. Our study shows that the self-renewal capacity of RGLs in the adult hippocampal dentate gyrus is highly dependent on the chloride importer NKCC1.

1-F-132: Extinction of conditioned memory modulation

Travis Francis[1], Francesco Leri[1]

[1]University of Guelph

It has been established that exposure to drug conditioned stimuli (CS) can enhance memory consolidation, indicating that drug CSs not only produce changes in behaviour, but can also impact cognition. Therefore, it is possible that conditioned memory modulation, like other conditioned responses, will display extinction. The current study used classical and operant conditioning techniques to test this hypothesis in male Sprague-Dawley rats performing an object location (OL) memory task. To establish the CS in Experiment 1, rats were injected with heroin (0, 0.3, 1 mg/kg, S.C.) and immediately placed in operant chambers for 1 hr, once a day for 5 consecutive days. It was found that exposure to the heroin-CS four days after conditioning dose-dependently enhanced object location memory. In addition, when tested after 6 exposures to the CS without receiving heroin, the CSs ability to modulate memory was significantly reduced. In Experiment 2, rats were trained to self-administer heroin (0.05 mg/kg/inf) on a continuous reinforcement schedule for 12 days. It was found that exposure to the heroin-CS four days after training enhanced object location memory, and when tested after 6 exposures to the CS without receiving heroin, the CSs ability to modulate memory was significantly reduced. Taken together, these results support the idea that conditioned memory modulation occurs in parallel with conditioned responses that are mediated by conditioned stimuli.

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1-F-133: The effects of maternal immune activation on early developmental milestones and behaviour in outbred CD-1 mice.

Ryan Wheeler[1], Michael Trim[1], Gabrielle Clark[1], Tamara Franklin[1]

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Maternal immune activation (MIA) in mice can be used to investigate the link between perinatal infection and early-life developmental disorders such as cerebral palsy and autism spectrum disorder. Studies have shown that adult mice exposed to a bacterial or viral immune response during early- to mid-embryonic development display reduced social communication and interaction, and increased repetitive stereotypic behaviour. To date however, few studies have looked at the effects of MIA on early behaviours and developmental milestones in mice. In the current study, pregnant CD-1 dams were injected at embryonic day 11.5 with either lipopolysaccharide (LPS) or polyinosinic:polycytidylic acid (PolyIC) to stimulate aspects of a bacterial or viral immune response, respectively. Offspring were then assessed from post-natal day 2-21 using a modified Fox developmental behavioural test battery to assess reflexive and morphological developmental milestones. Additionally, grooming, homing to maternal bedding, and activity/exploration in the open field were evaluated. Overall, accelerated development and alterations in behaviour were observed in the MIA mice compared to sham-injected controls. These results suggest that MIA results in differential physiological and behavioural characteristics that emerge during early post-natal development, and further highlight the need for research that focuses on the effects of MIA during this developmental period.

G - Novel Methods and Technology Development

1-G-134: Cortical neuroprosthetic intervention to recover movement after spinal cord injury: an overview of our translational program.

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Spinal cord injury interrupts the supraspinal control of leg movement. Most injuries are incomplete, thus residual connections between the brain and the spinal cord are spared and can be targeted to promote motor recovery. We designed a cortical neuroprosthetic platform, whereby microstimulation of the motor cortex is integrated and synchronized into locomotor behavior in real-time. In the rat and cat models we studied: 1) How does the motor cortex modulate walking and what control can be recovered after spinal cord injury, 2) What are the effects of long-term rehabilitation therapies targeting the motor cortex. We found that, in intact animals, cortical stimulation achieves high fidelity and proportional control of the swing trajectory of the contralateral leg. After a unilateral spinal cord injury, contralateral cortical stimulation promotes organized leg movements and alleviates motor deficits such as foot-drop. Long term training has beneficial effects on voluntary leg control. Ipsilateral cortical stimulation also alleviates motor deficits, targeting extension and posture. In contusive spinal cord injuries affecting both legs, alternate bilateral cortical stimulation

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alleviates bilateral deficits. Finally, combining cortical stimulation epidural spinal stimulation results in a beneficial synergy which improves the potential of each of the two techniques alone. This translational research can inform clinical rehabilitation practice. Our results advocate for a decisive cortical role in functional restoration of walking after SCI.

1-G-135: Investigating microstructural changes in white matter in multiple sclerosis: A systematic review and individual participant data meta-analysis of neurite orientation dispersion and density imaging

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Background: Multiple sclerosis (MS) is characterised by widespread damage of the central nervous system that includes alterations in normal-appearing white matter (NAWM) and demyelinating white matter (WM) lesions. Neurite Orientation Dispersion and Density Imaging (NODDI) has been proposed to provide a precise characterisation of WM microstructure. NODDI maps can be calculated for neurite density index (NDI), orientation dispersion index (ODI), which estimate orientation dispersion and neurite density. Although NODDI has not been widely applied in MS, this technique is promising in investigating the complexity of MS pathology, being more specific than diffusion tensor imaging (DTI) in capturing microstructural alterations.Aims: We conducted a meta-analysis of studies using NODDI metrics to assess brain microstructural changes and neuroaxonal pathology in WM lesions and NAWM in patients with MS.Methods: Three reviewers conducted the literature search of four electronic databases (Medline, Embase, Scopus, and PubMed). We performed a random-effect meta-analysis. The extent of between-study heterogeneity was assessed with the I2 statistic. Funnel plots and Egger's tests were used to assess publication bias.Result: We identified 7 studies analysing 374 participants (202 MS, 172 controls). NDI in WM lesions and NAWM were significantly reduced compared to healthy WM. The standardised mean difference was -3.08 (95%CI -4.22 to (-1.95), p=<0.00001, I2=88%) and -0.70 (95%CI -0.99 to (-0.40), p=<0.00001, I2=35%) respectively. There was no statistically significant difference of ODI in MS WM lesions and NAWM compared to healthy controls. The standardised mean difference was -0.44 (95%CI -1.60 to (-0.71), p=0.45, I2=95%) for WM lesions and -0.46 (95%CI -2.07 to (-1.15), p=0.58,

1-G-136: Testing available quantitative methods to analyze brain immune cell morphology

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Microglia are functionally dynamic brain immune cells known to adapt their morphology depending on their environment. These context-dependent morphologies are extensively measured to inform changes in function. However, current manual morphological analyses, while informative, are often time-consuming and fail to detect subtle differences in cell architecture. To solve these limitations, we tested the sensitivity of an open-source quantitative method to measure microglial morphology called Fractal Analysis, adapted into a manual analysis of cell perimeter and area. Using the automated FracLac Plugin (ImageJ), we calculated the fractal dimension (FD) and lacunarity (LA), complementary indices, of two

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sets of immunohistochemical stainings (fluorescent and non-fluorescent) of hippocampal microglia and infiltrating bone marrow-derived macrophages (BMDM) from healthy postnatal mice. By creating a macro, we were able to combine our manual methodology to the fractal analysis, and find that FD and LA were more sensitive to changes in morphology than measurements of area and perimeter. In our dataset, FD and LA were both significantly increased in microglia compared to BMDM, while only LA was significantly higher in microglia among the ventral compared to the dorsal part of the hippocampus, possibly indicating increased process ramification. The detection of these differences in healthy tissue emphasizes the diverse regional morphology of microglia compared with infiltrating immune cells, but also the sensitivity of this automated methodology to detect subtle morphological changes.

1-G-137: Development of a novel optogenetic based model of alpha-synuclein aggregation to study Parkinson's disease

Razan Sheta[1], Morgan Bérard[1], Maxime Teixeira[2], Walid Idi[1], Roxanne Turmel[2], Jérome Lamontagne[2], Denis Soulet[1], Francesca Cicchetti[3], Edward Fon[4], Abid Oueslati[2]

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Parkinson's disease is characterized by dopaminergic neuronal loss and presence of proteinaceous inclusions Lewy bodies. These inclusions are constituted of a pre-synaptic protein, alpha-synuclein. Evidence suggest for a central role of alpha-syn aggregation in PD. However, how these aggregates precipitate DA neuronal loss remain elusive. This is due to the lack of proper models to undertake such investigations. To overcome this limitation, our group created a cellular and animal model of PD mimicking authentic LBs features. Using our new optogenetic-inducible alpha-syn aggregation, we aim to dissect how these inclusions interfere with physiological functions of DA neurons leading to neuronal loss. Our optogenetic versatile strategy allows for spatiotemporal control of alpha-syn aggregation both in vivo and in living cells. This approach is based on the use of a mutant form of the Arabidopsis thaliana photoreceptor cryptochrome 2 (CRY2). When stimulated with blue light, CRY2 undergoes reversible and robust protein clustering. Fusing this system to alpha-syn, CRY2 clustering triggered aggregation of alpha-syn prompting formation of LB-like inclusions in living cells. We refer to this system as light-inducible protein aggregation (LIPA). LIPA has allowed for real-time induction of alpha-syn inclusions with remarkable spatial and temporal resolution both in vitro and in vivo. Results showed that LIPA-induced aggregates auto-perpetuate for several days, faithfully mimicking authentic features of LBs. Optogenetically induced alpha-syn aggregation in mice induced significant dopaminergic neuronal loss and behavioural impairment. LIPA provides a dependable and invaluable tool to generate, visualize and dissect the role of protein aggregates in neurodegenerative disorders.

1-G-138: Optogenetic-mediated spatiotemporal control of α-synuclein aggregation mimics Lewy body formation and triggers neurodegeneration

Morgan Bérard[1], Razan Sheta[1], Raquel Rodriguez-Aller[2], Roxanne Turmel[2], Maxime Teixeira[2], Walid Idi[1], Melanie Alpaugh[3], Jérome Lamontagne[2], Denis Soulet[1], Francesca Cicchetti[3], Armen Saghatelyan[1], Edward Fon[4], Abid Oueslati[2]

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α-synuclein (α-syn) aggregation into insoluble deposits, referred to as Lewy bodies (LBs) is the paramount pathological hallmark of Parkinson's disease (PD) and related α-synucleinopathies. However, how these aggregates affect neuronal homeostasis leading to neurodegeneration remains elusive. This gap in knowledge is mainly due to the lack of proper cellular and animal models to undertake such investigations. We have addressed this limitation by developing a light-inducible protein aggregation system (LIPA). This application is based on the use of a mutant form of the Arabidopsis thaliana photoreceptor cryptochrome 2 (CRY2), which when stimulated with blue light, mutant CRY2 undergoes rapid, reversible and robust protein clustering or aggregation. The use of this application allows for real-time induction of α-syn inclusions formation with remarkable spatial and temporal resolution in both cell culture and in vivo paradigms. We used a gene therapy approach, based on the use of adeno-associated virus (AAV), to overexpress our LIPA system directly into the brains of naive mice. For the delivery of the blue light necessary for the induction of the aggregation and propagation of α-syn, we used implantable micro-devices developed by Amuza Inc. We report on the development of a light-inducible protein aggregation (LIPA) system that enables real-time induction of α-syn inclusion formation with remarkable spatial and temporal resolution in living cells. In vivo, LIPA-α-syn aggregates compromised the nigrostriatal transmission, induced dopaminergic neuronal loss and PD-like behavioral impairment. Our system provides a novel, dependable and invaluable tool to generate, visualize and dissect the role of protein aggregates in PD and possibly other neurodegenerative disorders.

1-G-139: Generation of unique oligodendrocyte lineage cells following direct lineage reprogramming of reactive astrocytes

Justine Bajohr[1], Arman Olfat[1], Kevin Lee[1], Daniela Lozano Casasbuenas[1], Maryam Faiz[1]

[1]University of Toronto

Direct lineage reprogramming (DLR) is a novel strategy which converts one cell type to another without the need for a pluripotent intermediate. Oligodendrocyte (OL) loss is characteristic of many neurological conditions, and thus astrocyte to OL reprogramming is of interest for central nervous system repair. Given the differential loss of OLs and their progenitors following disease, it is important to be able to generate OL lineage cells at different stages of development. Here we show that astrocytes can be converted to various cells of the OL lineage in vitro when transduced with transcription factors (TFs) involved in OL fate determination. Using GFAP driven lentiviruses containing TFs of interest, postnatal (P1-P5) cortical astrocytes were transduced and assessed for markers of the OL lineage at varying time points. Ectopic expression of an early OL fate specification TF resulted in the conversion of approximately 18% of transduced astrocytes to Sox10+ induced oligodendrocyte progenitor cells (iOPCs). Ectopic expression of TFs involved later in OL development resulted in the conversion of approximately 12% of transduced astrocytes into O4+ induced OLs (iOLs). Live cell imaging of the reprogramming process confirmed that iOPCs and iOLs originate from S100ß expressing astrocytes. These findings demonstrate the DLR of astrocytes to cells of the OL lineage, and that this can be tailored to generate cells at different stages of maturity. These studies lay the groundwork for novel, DLR-based therapeutic strategies for diseases involving OL lineage cell loss.

1-G-140: Single cell RNA-sequencing analysis of regionally patterned human pluripotent stem cell-derived neural organoids

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Eloi Mercier[1], Leon Chew[1], Adam Añonuevo[1], Mark Hills[1], Allen Eaves[1], Sharon Louis[1], Erin Knock[1]

[1]STEMCELL Technologies

Advancements in the neural organoid culture system from the lab of Sergiu Pașca (Yoon et al., Nat Methods, 2019) were the fundamental technologies used in the STEMdiff Dorsal and Ventral Forebrain Organoid Differentiation Kits, recently launched, to generate brain-region-specific organoids representing the dorsal and ventral forebrain. To confirm that the new kits reproduced brain-region-specific organoids comparable to the published protocol, we sought to investigate the cellular diversity of these organoids using single-cell RNA sequencing, the gold standard in elucidating the cellular composition of complex tissues. We generated dorsal and ventral forebrain organoids and dissociated them into single-cell suspensions on day 50 for use in RNA isolation. Our results show that dorsal forebrain organoids contain a diverse array of cell types including glutamatergic neurons (40 - 60%; LHX2/TBR1/NEUROD6), radial glial cells (20%; TNC/HOPX), and neural progenitors (10%; LHX2/PAX6/TBR2), whereas ventral forebrain organoids contain GABAergic neurons (70%; NKX2.1/GAD1/VGAT/PBX3) and ventral progenitors (25%; NKX2.1/PBX3/ATP1A2). Our data further showed low intra-organoid variability. Comparative analyses revealed that the organoid cell composition and gene expression of key markers are consistent with those observed in organoids from published protocols and publicly available data for developing fetal brain tissue. Our results demonstrate that STEMdiff Dorsal and Ventral Forebrain Organoid Differentiation Kits can generate relevant in vitro models of the developing telencephalon and enable further study of the complexity of brain development and disorders.

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Poster Session 2

A – Development

2-A-141: Metabolic defects in brain endothelial cells from 16p11.2 deletion autism mice

Julie Ouellette[1], Shama Naz[1], David Patten[1], Baptiste Lacoste[2]

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Brain development and function are exceptionally reliant on the adequate development and maintenance of vascular networks. As such, early impairments in vascular health can lead to neurodevelopmental defects. Despite a wealth of knowledge on neuronal mechanisms of autism spectrum disorders (ASD), very few studies have considered the role played by the brain vasculature in ASD. ASD are viewed as neurodevelopmental conditions associated with genetic origins such as the common 16p11.2 deletion which leads to haploinsufficiency of 27 conserved genes. We undertook an extensive study to investigate the cerebrovascular contributions to ASD and revealed that 16p11.2 deletion induced endothelial-dependent structural and functional neurovascular abnormalities, establishing a novel vascular link to ASD. While this study associated dysfunctional endothelial cells (ECs) with 16p11.2 deletion syndrome, the endothelial aspects leading to these dysfunctions remain to be elucidated. We are using an untargeted metabolomics approach, as well as assessing mitochondrial function, to decipher core features of brain ECs isolated from a mouse model of 16p11.2 deletion syndrome. We identified an energetic failure in 16p11.2 deficient ECs compared to WT ECs, as shown by altered concentration of high energy metabolites involved in the Krebs cycle as well as in energy supply. This research program will provide new insight into key players in ASD pathogenesis, which is an essential pre-requisite for the development of transformative therapeutic strategies.

2-A-142: Capicua is required for the regulation of adult hippocampal neurogenesis

Brenna Hourigan[1], Spencer Balay[2], Graydon Yee[1], Saloni Sharma[1], Qiumin Tan[1]

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Adult hippocampal neurogenesis (AHN) is the process that generates neurons from neural progenitor cells (NPCs) in the adult hippocampus. AHN is important for proper learning, memory, cognition, and mood regulation but is severely decreased in memory and mood disorders. Understanding how AHN is regulated may lead to treatments for these conditions. AHN entails multiple cell stages involving NPC proliferation and differentiation, followed by neuron maturation. The transition of these cell stages is regulated by expression of specific transcription factors. We found that the transcription factor capicua (CIC) is expressed in NPCs but is downregulated during NPC differentiation. Contrastingly, CIC is upregulated during neuron maturation. Such expression changes suggest CIC might play a role in AHN. Here we find that deleting CIC in the hippocampus, including the adult hippocampal neuronal lineage, results in reduced NPCs due to increased differentiation into immature neurons. These immature neurons have impaired dendrite complexity and abnormal migration, with

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delayed progression to fully matured granule neurons. Together, our results show that CIC plays a critical role in NPC differentiation and neuron maturation in AHN. Our study identifies a previously unknown role for CIC in AHN. Given that decreased AHN is associated with mood and memory disorders, future investigations into the genes and pathways that CIC regulates may reveal crucial molecular inroads and therapeutic entry points into these conditions.

2-A-143: Investigation of the role of the β-arrestin signaling adaptors in Shh-mediated axon guidance

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During nervous system development, axons are guided to their correct targets by attractive and repulsive guidance molecules. In the developing spinal cord, Sonic hedgehog (Shh) is secreted by the floor plate and attracts axons of commissural neurons to the ventral midline. In axon guidance, Shh binds to its receptor Boc and activates downstream effectors such as Smoothened (Smo) which then activate Src-family-kinases (SFKs), which are required for axon attraction by Shh. However, we don't know how SFKs are activated by Smo. β-arrestins 1 and 2 are adaptor proteins known for their role in G-protein coupled receptor desensitization. They also interact with and regulate Smo in canonical Shh signaling and they can interact with SFKs for intracellular signal transduction. We hypothesized that β-arrestins act downstream of Smo in Shh-mediated axon guidance and are required for SFK activation. We found that β-arrestins are expressed in commissural neurons and that Smo, β-arrestins and SFKs interact in co-immunoprecipitation experiments. Moreover, SFKs only interact with Smo in the presence of β-arrestins, suggesting that β-arrestins act as a scaffold to recruit SFKs to Smo. Our preliminary results indicate that depleting β-arrestins in commissural neurons prevents Shh-mediated attraction. We will next determine whether β-arrestins are required for Shh-mediated SFK activation and test the requirement for β-arrestins in axon guidance in vivo by analyzing β-arrestins conditional knockout mice. My project would identify β-arrestins as novel scaffold proteins for axon guidance.

2-A-144: Quiescent and proliferative states of adult neural stem cells are characterized by different Ca2+ dynamics and steady-state intracellular levels.

Alina Marymonchyk[1], Archana Gengatharan[1], Marina Snapyan[1], Armen Saghatelyan[1]

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The adult brain has a remarkable capacity to produce new cells that migrate and integrate into pre-existing neuronal circuits throughout the lifespan of animals. Adult neural stem cells (NSCs) in subventricular zone (SVZ) are a largely quiescent population and their activation and proliferation is modulated by a number of physical and chemical cues from different sources. However, the mechanisms that integrate those signals and regulate quiescent/proliferative (Q/A) states transition are poorly understood. In this study, using ex-vivo calcium imaging, we revealed the universal Ca2+ signature that characterize activated (aNSCs) and quiescent (qNSCs) NSCs states. We showed that qNSCs are characterized by higher frequency of Ca2+ fluctuations and lower intracellular Ca2+ level, compared to aNSCs. This different Ca2+ dynamics were regulated by intracellular IP3-sensitive Ca2+

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stores. Pharmacological inhibition of IP3-sensitive stores decreased the frequency of Ca2+ fluctuations and increased intracellular Ca2+ level of qNSCs. Similarly, CRISPR-Cas9 mediated deletion of Itpr2, specifically in SVZ NSCs resulted in the same characteristic differences in the Ca2+ dynamics. Importantly, these changes were accompanied with increase in proliferation indicating a causal relationship between internal store-dependent Ca2+ dynamics and NSCs Q/A transition. We also showed that anti-proliferative pathways are keeping NSCs quiescent by modulating calcium dynamics. For instance, pharmacological inhibition of the melatonin signaling pathway activates NSCs by reducing the frequency of Ca2+ fluctuations and increasing intracellular Ca2+ levels. Altogether, our data suggest that Ca2+ signaling in NSCs may integrate and decode different signals to regulate NSCs Q/A transition.

2-A-145: Astrocyte-derived Hmgb1 is required for endfoot placement during postnatal brain development in mice

Moises Freitas-Andrade[1], Peter Van Dyken[2], Gareth Rurak[3], Gianfilippo Coppola[4], Cesar Comin[5], Luciano Da F. Costa[5], Natalina Salmaso[6], Baptiste Lacoste[1]

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After birth, the interplay between astrocytes and endothelial cells (EC) during cerebrovascular maturation is essential, yet the time course of these interactions remains elusive. Here, we leveraged pan-astrocytic gene Aldh1L1 as a molecular handle to unmask gliovascular dynamics in the postnatal mouse brain. Using mice with Green Fluorescent Protein expressed under the control of the Aldh1L1 promoter, coupled with EC and proliferation markers, we found a correlation between astrocyte and EC proliferation between postnatal days 0 (P0) and P14. Proliferation peaked at P4 and declined by P7, reaching low levels by P14. Immunofluorescence and electron microscopy approaches revealed that past P4, astrocytes undergo extensive maturation and interact with blood vessels only after P7 (mostly evident at P14) with their endfeet. To unmask the angiogenic influence of astrocytes on brain vasculature, Aldh1L1-EGFP-L10a mice (EGFP fused to ribosomal protein L10a) were used for translating ribosome affinity purification (TRAP) followed by RNAseq. Temporal changes in actively transcribed genes were measured during the first 3 postnatal weeks. Vascular endothelial growth factor (VEGF) expression increased soon after birth and remained elevated up to P14. Interestingly, expression of high-mobility group box 1 (Hmgb1), appeared very high at birth, then decreased by P14. Using conditional knockout approaches, we discovered that HMGB1 expression in astrocytes is essential for proper endfeet vessel coverage. Altogether, this study reveals novel players involved in gliovascular maturation.

2-A-146: Interleukin-1 cytokines as regulators of developmental microglia proliferation

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Microglia proliferate extensively in late embryonic and early postnatal life to achieve a stable homeostatic density. Microglia modulate several developmental processes, including the establishment of synaptic connections and the guidance of myelination. Insufficient microglia expansion unsurprisingly impacts these processes. The factor(s) that promote developmental proliferation (mitogens) remain unknown. Interleukin-1 (IL-1) cytokine expression overlaps temporally with developmental microglia proliferation and IL-1 signaling regulates microglia proliferation in non-developmental contexts. We find reduced microglia densities in the brain and spinal cord of early postnatal IL-1α and IL-1β knockout mice, though spinal cord microglia densities normalize to control levels by postnatal day 30 (P30). We also find elevated microglia proliferation in the P10 IL-1α knockout brain, possibly as a delayed compensatory affect. However, neither IL-1α nor IL-1β promotes microglia proliferation in culture. We therefore hypothesize that IL-1α and/or IL-1β guide developmental microglia proliferation by promoting microglia mitogen release from astrocytes, a cell lineage that alters secretion in response to IL-1 treatment. In culture, the astrocytes treated with either IL-1α and IL-1β release unknown factors that promote microglia proliferation. We are working to identify the microglia mitogen(s) present in astrocyte conditioned media and will identify how the mitogen(s) modulate developmental microglia proliferation in vivo.

2-A-147: Understanding the role of SYNGAP1 in GABAergic circuit development and function

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Haploinsufficiency of Syngap1 gene encoding the Synaptic Ras- GTPase Activating protein is associated with intellectual disability, autism spectrum disorder and epilepsy. Haploinsufficiency of Syngap1 leads to alterations in synaptic plasticity, behavioral abnormalities and cognitive deficits in mouse models. In particular, several studies have shown that Syngap1 regulates the time course of the maturation of dendritic spines and glutamatergic synapses in excitatory neurons; In contrast, the role of Syngap1 in inhibitory, GABAergic neurons is relatively uncharted. GABAergic neurons are a diverse class of neurons with different morphology, connectivity and physiological properties. They play an important role in neural circuit development and plasticity. 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 are involved in the synchronization of the firing rate of pyramidal cell populations. Our aim is to study the role of Syngap1 in PV cell development In vivo, in establishing balanced synaptic connectivity and proper network in contributing to the behavioral endophenotype and cognition in mouse model by techniques like immunolabelling the synapses and behavioral studies. Preliminary data suggest that alteration in synaptic connectivity of PV cells in different cortical regions do contribute to observed overall behavioral and cognitive deficits. A better understanding of the role of Syngap1 in GABAergic cell development may shed light on the involvement of GABAergic circuit alterations in the cognitive deficits caused by Syngap1 haploinsufficiency in humans.

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2-A-148: Transplanted astrocytes develop, mature, and survive long-term in the mouse cortex

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Astrocytes are involved in diverse and highly specialized functions in the brain. They display morphological and molecular heterogeneity that is reflective of the microenvironments in which they reside. Astrocytes also become reactive in many brain disorders and diseases, and contribute to disease progression. To better understand how astrocytes develop and specialize within brain microenvironments, we transplanted mouse astrocytes into the mouse cortex in the first postnatal week, and assessed their integration in the host brain at various time points. We found that transplanted astrocytes developed complex morphologies typical of cortical protoplasmic astrocytes and displayed tiling arrangements with astrocytes from the host brain. Also, at 110-130 days post-transplantation, transplanted astrocytes expressed the same levels of GLAST/EAAT1, GLT1/EAAT2, and GFAP as astrocytes in the host brain. Similarly, spatial territories covered by transplanted astrocytes displayed the same density of pre-synaptic terminals as territories covered by host brain astrocytes. Finally, transplanted astrocytes developed endfeet with high AQP4 expression that were tightly associated with capillaries, similar to what we observed with astrocytes in the host brain. Our results indicate that transplanted astrocytes successfully integrate and survive long-term within the mouse brain when transplanted in the immature cortex. These findings open the possibility of using transplanted astrocytes to monitor changes in brain activity/function, and potentially as therapeutic tool to tackle brain diseases.

2-A-149: Prenatal cannabis exposure alters the firing properties of adolescent ventral tegmental area dopamine neurons

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Though cannabis use during pregnancy has increased, our understanding of its effects on offspring is incomplete. Gestational THC injection studies found altered goal-directed behaviour and mesolimbic dopamine reward circuitry in offspring of various ages. To investigate whether oral cannabis exposure during pregnancy alters ventral tegmental area (VTA) dopamine neuron activity, mice were exposed to 5 mg/kg THC cannabis extract in peanut butter or peanut butter alone from GD0-PD10. Whole cell patch clamp electrophysiology was performed in VTA slices from adolescent (P42-P46) offspring. Maternal weight gain, food intake, litter size, frequency of miscarriages, or maternal behaviour in a pup retrieval test were not different between groups, suggesting the effects of cannabis are not secondary to poor maternal care or health. VTA dopamine neurons of male mice exposed to cannabis from GD0 to PD10 had a more depolarised resting membrane potential, increased spontaneous firing, decreased latency to fire, and increased after-hyperpolarisation potential height, but not width. In contrast, dopamine neurons from female mice had shorter after-hyperpolarisation potentials, without changes in resting membrane potential, spontaneous firing frequency or other firing properties. Consistent with previous injection studies, prenatal exposure to oral cannabis differently alters the firing properties of male and female VTA dopamine neurons. Future research will examine synaptic changes

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and the behavioural implications of cannabis-induced differences in VTA dopamine neuronal activity.

2-A-150: Identification of a direct BMP synaptic gene network controlling neurotransmission and synapse maturation

Robin Vuilleumier[1], Mo Miao[1], Sonia Giro[1], Stephane Flibotte[1], Tianshun Lian[1], Annie Collins[1], Sophia Ly[1], George Pyrowolakis[2], Pejmun Haghighi[3], Douglas Allan[1]

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Bone morphogenetic proteins (BMP) play critical roles in the regulation of synaptic growth, stability, neurotransmission and homeostasis of several neuronal subtypes; yet how BMP signaling controls these functions remains mostly unknown. Here, by combining Drosophila genetics with RNA-seq, transgenic enhancer validation, and computational discovery of Smad-binding BMP-activating elements (BMP-AE) and BMP-silencer elements (BMP-SE), we uncovered a BMP-responsive neurotransmission gene network that is directly controlled by retrograde BMP signaling in Drosophila motor neurons. Surprisingly, we found that the BMP-SE motif mediates BMP-dependent upregulation of neuronal gene transcription, similar to the BMP-AE. Exploring the underlying mechanism for this atypical activity, we found that the absence in motor neurons of Shnurri (Shn), a Smad transcriptional corepressor, switches BMP-SE repressive activity to activation. Further, by genome editing of identified BMP-AE and BMP-SE motifs in the genomic loci of synaptic genes, we demonstrate the functional importance of direct BMP input to those genes to regulate neurotransmission and synaptic maturation in vivo. Finally, our analysis of BMP target genes in motor neurons identifies a novel, presynaptically-expressed gene that we find is required for the presence of critical postsynaptic neurotransmitter receptors at the neuromuscular junction. Taken together, these results revise the concept of strict BMP enhancer and silencer elements, and demonstrates how the BMP signaling pathway directly regulates synaptic functions.

2-A-151: Modelling the neurodevelopmental disorder Sifrim-Hitz-Weiss syndrome using mouse genetics

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Several neurodevelopmental disorders are caused by mutations in single genes encoding chromatin remodellers. For instance, de novo mutations in Chd4 cause Sifrim-Hitz-Weiss syndrome (SIHIWES). This disorder is characterized by macrocephaly and intellectual disability, though this has not yet been recapitulated in current Chd4 mouse models, precluding mechanistic insight. Mice containing a floxed ATPase domain of Chd4 were crossed with Emx1-Cre mice to yield forebrain-specific conditional Chd4 knockouts and heterozygotes, or with CMV-Cre mice to yield germline Chd4 heterozygotes. We used immunohistochemistry to study Chd4 ontogeny, and identify potential defects in cell composition in our SIHIWES models. Mice were also run through behavioural tests to assess for potential variations in learning, social, and anxiety behaviours. We show that Chd4 co-stained with markers for neural progenitor cells (Sox2, Neurog2), neurons (Ctip2, Brn2), oligodendrocytes (Olig2), and astrocytes (Aldh1l1) during development. Preliminary results also suggest that germline heterozygotes might display increased cortical thickness, and that male germline heterozygotes might exhibit reduce anxiety during the open field test and

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increased velocity throughout testing, with the exception of the beam break test. This suggests that Chd4 is expressed across various cell types throughout development and that partial loss of Chd4 may impact cortex size and anxiety behaviours in male germline heterozygotes. This may help elucidate the genetic basis of specific Chd4 variants, including those noted in SIHIWES.

B - Neural Excitability, Synapses, and Glia: Cellular Mechanisms

2-B-152: Bright eyed and bushy processes: Astrocytes in sleep and stress

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[1]UdeM - CRCHUM

One of the hallmarks of stress related psychiatric disorders, such as anxiety and depression is perturbations in sleep. Recent efforts to understand the physiological mechanism underlying sleep homeostasis have revealed a surprising role for a type of non-neuronal brain cell, the astrocyte. Astrocytes regulate many complex behaviours including learning and memory, decision making, and sleep. This is achieved through intimate structural and functional relationships with neurons, permitting astrocytes to regulate neuronal activity and excitability through diverse means including the supply of energy substrates. This process has been shown to modulate neuronal activity in sleep centres of the brain (e.g Lateral Hypothalamus;LH), which rely on astrocyte metabolic networks to maintain physiological sleep wake cycles. These metabolic networks are also sensitive to stress associated elevations in blood glucocorticoids. Despite the clear role of astrocyte networks in influencing sleep and wake, the underlying mechanism remains unknown. Given that a multitude of stress related psychiatric disorders are accompanied by disruptions in sleep homeostasis, we hypothesise that astrocyte networks are influenced by stress hormones (glucocorticoids), which in turn influence sleep-wake cycles. To test this hypothesis, we firstly investigated the impact of distinct chronic stress paradigms on expression of key astrocyte proteins, observing alterations in gap junction channels, glutamate transporters, and cytoskeletal proteins in the LH. These data suggest functional changes in astrocytes in response to chronic stress. Currently, we are focusing on the specific role of astrocytic glucocorticoid receptors in mediating these changes, using combined pharmacological and genetic approaches.

2-B-153: Heterogeneous intrinsic and synaptic properties of cerebellar Purkinje cells

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The cerebellar cortex is well known for its homogeneous circuit architecture, which repeats across lobules. Overlaying this homogeneous circuitry is a marked heterogeneity in molecular expression pattern across and within cerebellar regions. However, understanding how the heterogeneous molecular expression patterns in the cerebellar lobules link to function is largely unknown. We aim to understand the functional consequences of molecular heterogeneity, both in terms of the cell's intrinsic firing properties and synaptic function using

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electrophysiology and molecular tools in mice. In the cerebellar cortex, the Purkinje cell (PC) is the sole output neuron, and thus its spiking properties have a key influence on cerebellar output. In addition, plasticity at synapses onto PCs is essential for cerebellum-dependent learning. Our results demonstrate that in two lobules with widely different functions, there was a diverse range of spiking properties, which varied between lobules. These differences in spiking properties imply differences in underlying ion channels and consequent differences in the input-output response of the PCs in the two lobules. We also observed that excitatory synaptic currents at parallel fiber-Purkinje cell synapses (one of the two main inputs to the PCs) were different between regions. This difference in synaptic currents is such that synaptic plasticity in the two lobules is likely to use different signaling pathways. These results suggest that the cerebellum utilizes heterogeneous forms of information processing and plasticity to implement its varied behavioral functions.

2-B-154: Astroglial ionotropic NMDA receptor calcium signalling and modulation of cortical neuron activity

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Astrocytes express different neurotransmitter receptors that serve to integrate these cells into neuronal networks. Many of these receptors, when sensing neuronal activity, induce elevations in intracellular astrocyte Ca2+, which leads to the release of gliotransmitters that modulate nearby neurons. Ionotropic N-methyl-D-aspartate (NMDA) receptors are found on astrocytes and are activated by glutamate and D-serine or glycine, and conduct Ca2+ into astrocytes. In brain slices, astrocyte NMDAR activation causes depolarization and Ca2+ elevations. However, its role in astrocytes Ca2+ transients and feedback modulation to neurons in vivo is not characterized. Therefore, we used a novel NMDAR knockdown (KD) construct to reduce NMDAR expression specifically in cortical astrocytes. Then, using dual calcium imaging of astrocytes and neurons each expressing a unique genetically encoded calcium indicator (Lck-GCaMP6f and RCaMP1.07 respectively) we determined the impact of astrocytes NMDARs on astrocytes Ca2+ transients and nearby neuronal activity. Two-photon microscopy of the barrel cortex of awake mice revealed that NMDAR KD reduced Ca2+ responses to whisker stimulation in both astrocytes and neurons. This highlights the importance of NMDAR in astrocyte Ca2+ signalling and astrocyte-neuron communication and suggests that astroglial NMDAR KD could cause deficits in sensory perception. This work contributes to a deeper knowledge of mechanisms underlying astrocyte Ca2+ signalling and provides novel directions to study the role of astrocytes in neuronal circuits.

2-B-155: Transient spike initiation supports digital information transfer in axons: simulations in a biophysically detailed model

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Spikes are usually initiated at the axon initial segment (AIS), the most excitable site of a neuron. Yet other regions of the neuron are also excitable. While there are many studies on somatic and dendritic excitability, axon excitability has yet to be thoroughly investigated in most neurons because the small size of the axon precludes intracellular recordings. Using a novel optogenetic approach, recent experiments from our lab have shown that axon spikes

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transiently in response to sustained depolarization. Although the optogenetic method has many advantages, it still has some limitations: first, light is not focused on one point, meaning stray light may hit other regions of the neuron; second, since voltage changes are recorded from the soma, the location of spike initiation must be inferred indirectly. These experimental limitations necessitated simulations to definitively interpret the experimental results. We built a multicompartment model of a CA1 pyramidal neuron with a detailed myelinated axon that reproduced our experimental data. The model confirmed the site of spike initiation based on the shape (kinkiness) of spikes recorded in the soma. Simulations also confirmed that even when targeting the axon for photostimulation, a small degree of stray light can hit the dendrites and evoke spikes in the AIS. The results ultimately confirm that the AIS spikes repetitively during sustained depolarization, consistent with analog to digital transduction of information, whereas the axon responds with transient spiking only during abrupt changes in depolarization. Simulations show that the stimulus the axon receives during spike propagation is a very intense and short depolarization, which is precisely the input to which it is tuned to respond.

2-B-156: The contribution of calcium ion channels to brain pericyte calcium signaling in vivo

Jessica Meza Resillas[1], Michael Stobart[1], John Del Rosario[1], Megan Rodriguez[1], Noushin Ahmadpour[1], Jillian Stobart[1]

[1]University of Manitoba

Brain mural cells are important for the regulation of cerebral blood flow (CBF) and they participate in endogenous pathways like vasomotion and neurovascular coupling that direct CBF to highly activated areas of the brain. Pericytes are spatially isolated mural cells embedded on brain blood vessels and have possible contractile capacity; however, recent studies have identified different types of pericytes that differ in morphology and protein expression, creating a debate on their functional roles in CBF control. We evaluated the calcium signaling and hemodynamic influence of distinct pericyte populations: ensheathing pericytes and capillary pericytes, using transgenic mice with expression of genetically encoded calcium indicators (GCaMP6s and RCaMP1.07) in different pericyte types. Intracellular calcium signals were visualized via two-photon microscopy in brain slices and in vivo. By targeting different ion channel pathways pharmacologically, we found that ensheathing and capillary pericytes have different basal calcium pathways and different roles in hemodynamics at rest and during sensory stimulation to evoke neurovascular coupling. Our data provides novel insight into brain pericyte calcium signaling mechanisms and opens new avenues to clarify the role of pericytes in the regulation of CB. This may also contribute to the understanding of cerebrovascular and neurodegenerative diseases, like stroke, cerebral hypoperfusion or Alzheimer's disease, in which their pathogenesis remains to be fully elucidated.

2-B-157: Activation of a cortico-thalamic neural circuit attenuates renewal in male and female rats

Alexa Brown[1], Nadia Chaudhri[1]

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Contexts associated with prior reinforcement can renew extinguished conditioned responding. Both the infralimbic medial prefrontal cortex (IL) and paraventricular nucleus of the thalamus (PVT) are implicated in this renewal effect. Here we examined if connectivity between these regions, namely an IL-to-PVT neural circuit, was involved in renewal. We trained male and female Long-Evans rats to associate a conditioned stimulus (CS; 10 s white noise) with the delivery of a 10% sucrose unconditioned stimulus (US; 0.2 mL/CS) to a fluid port in a distinct context (Context A; 14 trials/session; 12 sessions). We then extinguished responding by presenting the CS without the US in a different context (Context B; 14 trials/session; minimum 2 sessions). At test, we used optogenetics to unilaterally stimulate IL-to-PVT neurons during CS presentations (473 nm; 5 ms pulses at 20 Hz for 10.2 s) in Context A under extinction conditions. Optically stimulating the IL-to-PVT in rats expressing Channelrhodopsin-2 with enhanced yellow fluorescent protein (ChR2-eYFP) significantly attenuated renewal of CS-elicited port entries compared to rats expressing eYFP alone, and this effect was equivalent in males and females. Further, rats expressing ChR2-eYFP (1) nose-poked significantly more for optical self-stimulation of the IL-to-PVT, and (2) expressed greater Fos density (a marker of neural activity) in the IL and PVT. These results demonstrate a compelling, sex-independent role of the IL-to-PVT neural circuit in mediating renewal of appetitive Pavlovian conditioned responding following extinction.

2-B-158: Impact of ependymal cell metabolic perturbation on brain function

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Metabolic regulation is thought to be an important feature within stem cell niches. Recent work suggests that ependymal cells (ECs), that line the ventricular system of the brain, could be critical players in regulating the ventricular-subventricular zone (V-SVZ). ECs are multi-ciliated glial cells that are responsible for regulating the neural stem cell niche and propelling the cerebrospinal fluid. Transcriptional profiling of the adult SVZ niche showed that ECs are highly enriched in glucose transporter 1 (GLUT1), leading us to hypothesize that ECs may regulate NSC behavior by modulating metabolism within the V-SVZ. To test this, I performed a conditional deletion of GLUT1 in adult ECs in vivo using aSMACreERT2:ROSATdTomato:GLUT1flox/flox mice to delete GLUT1 in aSMA+ ECs. At 1-month post-GLUT1 deletion, an increase in overall proliferation (marked with Ki67) was observed within the V-SVZ niche. A sex dimorphic effect was observed on neurogenesis; with females displaying a reduction in the number of DCX+ neuroblasts, while males exhibited no change. Interestingly, this reduction was more pronounced in the anterior V-SVZ compared to posterior V-SVZ, suggesting sensitivity to GLUT1KO might be spatially dependent. There was also a marked increase in GFAP staining and an accumulation of lipid droplets within the V-SVZ post-GLUT1 deletion suggesting that disruption in glucose metabolism may perturb local lipid metabolism. Altogether, these results indicate that EC metabolism regulates the NSC niche and may play a broader role in maintaining brain homeostasis.

2-B-159: Components of functional hyperemia are differentially modulated by locomotion and constrained by vasomotion in awake mice

Govind Peringod[1], Linhui Yu[2], Kartikeya Murari[1], Grant Gordon[3]

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Neural activity underlying sensation, movement or cognition drives regional blood flow enhancement - termed functional hyperemia - to increase the oxygen supply to respiring cells for as long as needed to meet energy demands. However, during sustained activation, whether functional hyperemia has distinct temporal and spatial components that are differentially regulated remains unclear. Using widefield intrinsic optical signal imaging in awake, head-fixed but active mice, we demonstrated biphasic changes in tissue oxygenation in response to 30s whisker stimulation. We found that the late component (20-30s), but not the early component (1-5s), was strongly influenced by level of whisking/locomotion in the region of highest response and in surrounding regions. Optical flow analyses revealed complex yet stereotyped spatial properties of the early and late phases that were related to location within the optical window and the initial state of the cerebral vasculature. Testing the impact of a direct vascular manipulation on biphasic functional hyperemia, we discovered that a low-dose of systemic Compound 21 in mural cell Gq-chemogenetic mice drove rhythmic hemodynamic oscillations at 0.1Hz. This state strongly limited both the magnitude and spatial extent of the sensory-evoked hemodynamic response, suggesting that vasomotion and functional hyperemia are inversely related. These data provide new insights into the cerebral microcirculation in the awake state and may have implications for interpreting functional imaging data.

2-B-160: SARS-CoV-2 infects human astrocytes and impairs neuronal viability in vitro

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Astrocytes are key regulators of brain homeostasis and are strongly associated with neurons, to which they provide metabolic support. COVID-19, initially reported as a disease of the respiratory system, is now known to affect the central nervous system, where it has been linked to the manifestation of astrogliosis. Over 30% of COVID-19 patients exhibit neuropsychiatric and neurological symptoms, yet cellular and molecular aspects of SARS-CoV2 infection in individual brain cell types remain largely unknown. Here, we attempt to gain further insight into the neuropathological consequences of SASR-CoV2 in vitro infection of astrocytes. We infected astrocytes derived from human neural stem-cells and assessed their proteomic and biochemical profile as well as the impact of the infection on the survival of stem-cell-derived neurons. We found that human astrocytes are susceptible to SARS-CoV-2 infection in vitro. In addition, infected astrocytes manifest changes in energy metabolism and in key proteins and metabolites used to fuel neurons and in the biogenesis of neurotransmitters. Finally, SARS-CoV2 infection elicits a secretory phenotype in astrocytes that reduces neuronal viability. Our data supports a model in which SARS-CoV-2 presents brain tropism, infects astrocytes and consequently leads to neuronal death or dysfunction. These processes are likely to contribute to the neurological symptoms seen in many COVID-19 patients.

2-B-161: Laminar and sex- specific expression of GluN2A, GluN2B and GluN2D NMDA receptor subunits within the dorsal horn of male and female rat spinal cord

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N-methyl-D-aspartate receptors (NMDARs) are excitatory ionotropic glutamate receptors expressed throughout the central nervous system (CNS), including in the dorsal horn (DH) of the spinal cord. The GluN2 subunits of NMDARs, GluN2A, 2B and 2D, confer NMDARs with structural and functional variability, enabling heterogeneity in synaptic transmission and plasticity. Despite essential roles for NMDARs in physiological and pathological pain processing within the DH, the distribution and function of specific GluN2 isoforms across DH laminae remains poorly understood. Furthermore, surprisingly, GluN2 expression in female rodents has been completely overlooked. We therefore investigated the relative expression of specific GluN2 variants in the L4/L5 lumbar DH of both male and female rats. With the aim to detect also the synaptic GluN2 isoforms that are expressed in the DH (GluN2A, 2B and 2D), we used pepsin antigen-retrieval to unmask these highly cross-linking protein complexes. We discovered that GluN2B and GluN2D were preferentially localized to superficial regions of the DH in males, while only GluN2B was predominantly expressed in the superficial DH of female rats. Moreover, unexpectedly, we identified an elevated expression of GluN2B in the medial division versus the lateral division of the superficial DH, in males only. These sex-specific localization patterns of GluN2-NMDAR subunits have significant implications for the understanding and treatment of pain and are relevant for future translational studies in human spinal cord tissue.

2-B-162: The role of Per2 on mood and alcohol related behaviours in males and females

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Various biological functions in organisms, ranging from the level of gene expression to physiological and behavioral processes, undergo daily variations generated by endogenous circadian clocks. Disruptions to circadian clock gene expression in the striatum were associated with depressive- and anxiety-like conditions, as well as abnormalities in reward-related processes. Recent findings in our lab show that the conditional knockout of the core clock gene Period2 (Per2) in the striatum alters ethanol consumption in a sexual dimorphic manner, but has only minor effects on mood- and anxiety related behaviors. Originally, it has been suggested that the nucleus accumbens (NAc), located in the ventral part of the striatum, is strongly involved in the control of the above-mentioned neuropsychiatric conditions, which are known to establish comorbidities. To further disentangle the role of Per2 on the pathophysiology of mood and anxiety disorders and alcohol abuse, Per2-floxed male and female mice received bilateral intracerebral injections of adeno-associated viral vectors expressing Cre-recombinase and eGFP or control vectors expressing eGFP only and were tested in a battery of behavioral assays to evaluate depressive- and anxiety-like behaviors, as well as alcohol consumption. Preliminary results suggest Per2- knockouts specific to the NAc consume more ethanol than controls, but has no effects on anxiety- and depressive-like behaviors. Further studies including gene expression analyses are needed to elucidate the underlying mechanisms driving these altered ethanol drinking behaviors in striatal Per2 knockout mice.

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2-B-163: Enhancing potassium-chloride co-transporter-2 (KCC2) function in neurons by targeting protein-protein interactions

Vineeth A Raveendran[1], Jessica Pressey[1], Satra Nim[1], Carles Corbi-Verge[1], Philip Kim[1], Melanie Woodin[1]

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

2-B-164: An investigation into an anomalous pyramidal cell type: atypical morphology and sustained cellular activity to novel stimuli

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Introduction: This research investigates an anomalous pyramidal cell type, dubbed "deep cells" in the subiculum of the hippocampus. Deep cells are structurally unique in that they completely lack radial oblique dendrites. This work will use in-vivo calcium imaging to elucidate how this remarkable change in structure effects neuronal function in vivo in the subiculum and its possible role during behaviour. Methods: Our lab has constructed a transgenic cre line to access this deep cell type. I use this mouse line to image deep cells during spatial navigation and novel object tasks. During these experiments, I use wire-free 1-photon miniscopes to image the dorsal subiculum while mice undergo an open field task with two local objects, repeated over several timepoints. Results: Data from this project show that deep cells act on very slow timescales and have robust, sustained activity that appear to 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 by day four. Intriguingly, this cellular signature is still reduced 100 days after initial introduction. In comparison to control cells, deep cells show novel object-centered activity and no classic spatial phenotypes expected from pyramidal cells in the subiculum. Conclusion: This data leaves us with intriguing evidence of a seemingly spatially uninvolved, novelty driven and

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morphologically distinct cell type previously undescribed in the subiculum. Future work will be integral to identifying the role of this cell in memory processes/dysfunction and the role of this novel cell type in other brain regions.

2-B-165: Activity-dependent changes in the hippocampal palmitoylome

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The formation and remodeling of synaptic contacts requires the precise distribution and trafficking of proteins to specialized compartments. Recent work demonstrates that post-translational modifications, including protein S-acylation, play a key role in strengthening and weakening of synaptic connections, known to underlie the cellular basis of learning and memory. To determine how the dynamic palmitoylation of neuronal proteins contributes to synapse plasticity, we utilized an unbiased, proteomic approach to identify 121 hippocampal proteins that were differentially palmitoylated 1 hour after a hippocampal-dependent fear conditioning learning paradigm. Gene Ontology analysis revealed that majority of proteins that exhibited an increase in palmitoylation in the fear conditioned group compared to control were synaptic proteins involved in neurotransmission and plasticity, whereas those that exhibited decreased palmitoylation were primarily involved in metabolic functions. We further validated activity-induced differential palmitoylation of a subset of the 121 identified proteins in vitro and then investigated the role of dynamic palmitoylation on the function of a validated protein, lipid phosphate phosphatase-related protein 4 (LPPR4-also called plasticity-related gene 1, PRG-1). We identified cysteine residues in PRG-1 that are palmitoylated and found that palmitoylation at these sites is important for spine formation. Furthermore, we show that activity-mediated PRG-1 palmitoylation alters the phospholipid processing function of PRG-1 and is essential for activity-induced insertion of AMPA receptors into the post-synaptic membrane. Together, this study identifies networks of synaptic proteins whose dynamic palmitoylation may play a central role in learning and memory.

2-B-167: The cellular landscape of the retrosplenial cortex

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Introduction: The retrosplenial cortex (RSC) participates in many higher-order cognitive functions and is host to many neurons with complex firing properties. However the organizational principles of this region, which underlies a multiplicity of functionality, are not well defined. The aim of this project is to employ a bottom-up approach in order to resolve the cellular composition of the RSC. Our hope is to generate a multi-level, comprehensive view of the mechanisms underlying RSC functionality from molecules, to cells, and circuits. Methods: We utilized a combination of single cell RNA sequencing and multiplexed in situ hybridization in order to reveal the identity and organization of transcriptomically unique subpopulations of neurons within the region. Using retrograde AAV tracing, we are mapping the long range projections of cells in the region. Results: We uncovered 9 unique subpopulations of excitatory neurons within the RSC. Contrary to canonical thought on gene

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expression and cell identity within the cortex, we found that the RSC exhibits finer-grained changes than expected from a cortical region.

2-B-168: Spatially patterned excitatory neuron subtypes and circuits within the claustrum

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

2-B-169: Aβ-dependent alteration of astrocytic GLT1 expression can trigger the multistage progression of Alzheimer's disease

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At the onset of Alzheimer's disease (AD), accumulation of oligomeric amyloid-β (Aβ) correlates with local hyperexcitability, possibly due to dyshomeostasis of extracellular glutamate. However, the interplay between Aβ oligomers and extracellular glutamate accumulation remains unresolved. We use an in silico approach to characterize the putative underpinnings of Aβ-dependent modulations of extracellular glutamate. We first consider how Aβ modifies the expression of astrocytic glutamate transporters (GLT1) and how it impacts extracellular glutamate time course. Accordingly, we develop a mathematical model for glutamate diffusion and uptake at synaptic terminals and their surroundings. Our model predicts that above a threshold Aβ concentration, astrocytic GLT1 transporters cannot prevent the accumulation of extracellular glutamate. This, in turn, promotes a positive feedback on synaptic glutamate release that favors excitotoxicity and neuronal hyperactivity.

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Next, we complement our model including calcium-dependent Aβ production and glutamate release. The interaction of multiple positive feedback loops of signaling can account for different tissue states, overcoming the traditional dichotomy of healthy and excitotoxic conditions. Specifically, changes in the basal firing activity can promote intermediate conditions useful to either predict AD's degeneration or offer new therapeutic perspectives. Our results support the notion of AD as a multistage pathology where transitions can follow multiple pathways, such as Aβ accumulation, excitotoxicity, or calcium dysregulation.

2-B-170: Active decay of long-term potentiation is regulated by PP2B, NMDA receptors and GluA2 trafficking within the hippocampus

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Forgetting is broadly considered a pathological response to advanced aging and neurodegenerative disorders. However, a growing body of evidence suggests that forgetting may help maintain neural circuits in a flexible state, conducive to memory formation. This suggests that forgetting may be an active process, supported by intrinsic, dedicated mechanisms. Through studying how Long-term potentiation (LTP), a leading cellular model for memory, "decays" over time, we sought to characterize how synapse strength may be actively reduced as a proxy for understanding forgetting. Using slices of mouse hippocampus, a brain structure required for memory formation, we recorded synapse responses in area CA1 after inducing a decaying form of LTP. LTP decay required ongoing neuronal activity as turning off stimulation maintained LTP in a potentiated state. We next hypothesized that NMDA receptors are required for LTP decay. Application of the broad-spectrum NMDA receptor antagonist AP5 following LTP induction reduced LTP decay, suggesting that calcium signaling may be involved. Thus, we next inhibited the calcium-dependent phosphatase, calcineurin (PP2B) which similarly limited decay. AMPA receptor complement is a primary determinant of synaptic strength and these receptors are dephosphorylated by PP2B. Consistent with this, preventing AMPA receptor internalization with the TatGluA23y peptide reduced LTP decay. Collectively, these data support the conclusion that LTP decay is driven by activity-dependent signaling cascades that couple to AMPA receptor regulation. These findings have implications for understanding the nature of forgetting, forming the basis for new therapeutic strategies that reduce exaggerated memory loss associated with neurodegenerative disorders and aging.

2-B-171: Supralinear integration in the prefrontal cortex: consequences of genetically-disrupted NMDA receptors

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Supralinear integration of glutamatergic inputs requires NMDA receptors (NMDAR) to generate dendritic plateau potentials. This integrative phenomenon promotes burst-firing, translating patterns of input stimulation into stronger behavioural output. However, it is not clear how deficient or variant NMDARs affect the generation of dendritic plateau potentials, despite the relevance of this question for autism spectrum disorders, schizophrenia, and rare disorders caused by de novo mutations in the GRIN genes encoding NMDAR subunits. Here, we examined the consequences of NMDAR disruption for supralinear integration in specific

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transgenic mouse models with aberrant expression of the obligate Grin1 NMDAR subunit, including a mouse with minimal expression and others heterozygous for human patient-specific genetic variants. Patch clamp electrophysiology in layer 5 neurons of the prefrontal cortex was used to characterize NMDAR-dependent plateau potentials evoked by electrical stimulation. These experiments revealed profound changes in NMDAR-dependent plateau potentials and their relationship with burst-firing. In particular, we illustrate the severe disruption in the nature and timing of the spiking output and also investigate aberrant compensatory increase in currents through ion channels normally kept in check by fully functional NMDA receptors. Ongoing work is testing pharmacological strategies to restore NMDAR signaling toward normalizing supralinear integration.

2-B-172: Assessing dendritic integrity and spine morphology following impact in the porcine cortex

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Dendritic spines are responsible for relaying excitatory input and regulating signalling between neurons and their morphology can give insight into synaptic function. Excitotoxicity brought on by brain injury results in synaptic dysfunction, as intracellular Ca2+ increases. This increase in intracellular Ca2+ over-activates various cellular kinases and proteases responsible for microtubule stabilization. Previous work in our lab has shown that after an impact, there is an increase in tensile strain within the depths of the porcine cingulate sulcus. Moreover, there was a marked decrease of the microtubule stabilizing protein MAP2 specifically within the apex of the sulcus. In our current work, we explored whether changes in spine morphology were associated with our impact model. The Golgi-Cox staining method was used to visualize dendritic spine morphology. Following impact, coronal slabs were placed into Golgi-Cox solution for 2 weeks. Cortical pyramidal neurons within the sulcus apex and arm were reconstructed. Preliminary data revealed a shift towards mushroom-type spines, compared to thin and stubby-type spines within the sulci of the brain after impact. These findings suggest a shift towards an excitatory synapse shortly after impact. Along with our previous findings of changes in MAP2 properties, the shift towards an excitatory synapse could implicate activation of kinases and proteases responsible for regulating MAP2 dynamics and altering spine morphology.

2-B-173: Repeated traumatic brain injury causes diffuse microvascular damage and impairs bidirectional synaptic plasticity

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Repeated mild traumatic brain injury (rmTBI) disrupts hippocampal function and can lead to long-lasting episodic memory impairments. We hypothesized that these deficits could arise as a result of microvascular damage and microglia activation leading to impaired synaptic plasticity. Using our Awake Closed Head Injury (ACHI) Model for repeated (8x over 4 days) head injury, we found that animals showed impaired neurological function after the first hit, that was sustained throughout all 8 impacts. Histological analysis showed that animals

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experienced diffuse microbleeds in the brain, including the hippocampus, and that this was accompanied by fibrinogen release and microglia activation. Furthermore, animals that experience rmTBI showed impaired bilateral synaptic plasticity, with the magnitude of both long-term depression (LTD) and long-term potentiation (LTP) of synaptic efficacy being impaired in the hippocampus. This work indicate that rmTBI can produce diffuse microbleeds, microglia activation, and impaired synaptic plasticity, giving insights into the mechanisms that can underlie the memory impairments that can accompany rmTBI. This work was supported by grants from the Canadian Institutes for Health Research (CIHR) to BRC.

2-B-174: Amyloid beta oligomers sensitizes Panx1 activation by NMDAR via ER resident STIM proteins

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[1]University of Manitoba

Loss of Ca2+ homeostasis is a key neurotoxic event underlying Alzheimer's disease pathology. Herein, amyloid-β oligomers (AβOs) provoke aberrant activation of Ca2+ permeable NMDA receptor (NMDARs) and sensitize Ca2+ release through endoplasmic reticulum (ER). Altered ER Ca2+ release dynamics caused by AβOs is sensed by the stromal interacting molecules (STIMs), which are known to activate surface expressed Ca2+ permeable channels through protein-protein interactions. Past studies have shown that overactivation of NMDARs activate pannexin1 (Panx1) channels. We now show that Panx1 activation is augmented by AβOs. Cultured hippocampal neurons from CD1, Panx1 WT and Panx1 KO mice were used for electrophysiological recordings. First, we show that excitatory synaptic deficits induced by AβOs require Panx1. Moreover, Panx1 activation by NMDARs, facilitated by AβO treatment, is reduced in STIM knockdown neurons. To establish the mechanism of Panx1 activation by STIM, we generated Panx1 mutants with deletions targeting intracellular N- and C-term domains. Our results show that a domain within the N-term of Panx1 is required for activation by STIM. Further, NMDAR-dependent Panx1 activation was eliminated in cultured neurons expressing a Panx1 mutant unable to bind STIMs. To conclude, our study is first to report the importance of the Panx1-STIM interaction in regulating activity of Panx1 channels downstream of NMDARs. Future investigations aim to develop potential therapeutic targets within our discovered region to modulate Panx1 activity and impede detrimental effects of AβOs.

2-B-175: Microglia derived extracellular vesicles propagate pro-inflammatory signaling via NLRP3 priming

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Dysregulated immune signaling in aging is characterized by abnormal microglial activity that can be detrimental to brain homeostasis if sustained. Aged microglia upregulate NFκB and NLRP3 inflammasome-mediated release of pro-inflammatory cytokines. The mechanisms driving this increase in aged microglia activity remain unclear. This study investigated the role of extracellular vesicles (EVs) as propagators of microglia signaling. To blunt this signaling we tested potential anti-inflammatory effects of cannabidiol (CBD) on EV-mediated microglia activation. EVs from untreated or LPS treated (500 ng/µl) BV2 cells were applied to

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naïve BV2 cells for 3 hours +/- ATP (1 μM) treatment. Cell lysates and RNA were collected after 3, 6, and 9 hours. In CBD experiments, cells were pre-treated with CBD (0.5 μM) for 3 hours. EVs derived from LPS-treated cells carry increased levels of IL1β and IL6 mRNA. Following treatment with LPS-treated EV, naïve cells significantly upregulate transcription of IL6, IL1β, iNOS and NLRP3. Western blot confirmed upregulation of pro-IL1β following LPS-EV treatment and active caspase-1 after additional ATP treatment. Pre-treatment with CBD significantly reduced transcription of IL1β and IL18 in EV treated cells. EV-mediated pro-inflammatory signaling may represent a novel mechanism whereby age-related enhanced microglial activity is propagated. Future work investigating EV-mediated propagation in vivo, and the potential role of CBD as a modulator of this activity, will improve our understanding of age-related microglia signaling.

2-B-176: Exploring neurodifferentiation and maturation process of iPSCs derived from schizophrenia patients with multimodal optical microscopy

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Schizophrenia (SZ) is a serious mental disorder characterized by hallucinations, delusions, and impaired cognitive behavior. Substantial heterogeneity in the clinical phenotypes complicates its diagnosis and treatment. The pathogenesis results from a complex interaction between genetic vulnerability and environmental factors, altering neuronal development particularly. Indeed, several genes and proteins associated with neurite growth, neuronal migration, and synaptic development are altered in SZ. However, the processes of neurodifferentiation and functional maturation of neuronal networks are still largely unexplored. Therefore, the exploration with multimodal optical imaging tools of the in vitro of cortical neural cell generation using iPSCs from SZ patients and controls will help measure the maturation and organization of these cultured neuronal networks. Human iPSCs lines were differentiated into mixed cortical neural cells and characterized by flow cytometry, immunostaining, western blot, and patch-clamp techniques. To explore functional and morphological properties, we use quantitative phase digital holographic microscopy (QP-DHM) combined with fluorescence imaging. QP-DHM is a high-resolution, non-invasive technique allowing to assesse cell structure and dynamics with axial sensitivity at the nanoscale. These tools will serve to explore the excitatory and inhibitory (E/I) balance of these cultured neural networks. Such a multimodal imaging approach coupled with human iPSCs disease models holds great promises to identify cellular risk biomarkers for major psychiatric disorders, including schizophrenia.

2-B-177: Effect of fasting on lateral hypothalamus GABA to ventral tegmental area GABA synapses

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The ventral tegmental area (VTA) contains a heterogenous population of GABA neurons, making up about 30% of cells in the VTA. These GABA neurons regulate the activity of VTA dopamine neurons, affecting the release of dopamine in the nucleus accumbens (NAc). The

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release of dopamine in the NAc plays an important role in energizing goal directed behaviour towards food. GABA neurons, projecting from the lateral hypothalamus (LH), have been shown to preferentially synapse with VTA GABA neurons. Activation of LH GABA disinhibits the VTA GABA circuit to stimulate the release of dopamine in the NAc, resulting in consummatory behaviour. Acute fasting (AF) increases the incentive motivation for food. Despite the LH GABA to VTA GABA circuit being a powerful driver for food consumption, how it is affected by AF is unknown. Using patch clamp electrophysiology in midbrain slices expressing channelrhodopin in LH GABAergic terminals in the VTA, we demonstrate that following AF, LH GABA neurons have reduced inhibition of VTA GABA neuronal firing. Through train stimulations and strontium-induced asynchronous release, we show that this weakening of the LH GABA input is due to a scaling down of inhibitory postsynaptic current (IPSC) responses. Following AF, release probability of GABA from LH GABA neurons is decreased in female by not male mice. Taken together, these results show that the LH GABA to VTA GABA circuit is affected by acute energy deprivation and that males and females respond differently.

C - Disorders of the Nervous System

2-C-178: Microglia and monocyte-derived macrophage contribution in myelin debris clearance during remyelination

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Multiple sclerosis is a demyelinating disease. Despite the successes in reducing disability, regenerative therapies are lacking. Remyelination is a regenerative process, associated with lower disability. Remyelination necessitates the clearance of inhibitory myelin debris, which is impaired in MS. Myelin debris is mainly phagocytosed by CNS resident microglia and monocyte-derived macrophages (MDMs). However, it is unknown to what extent microglia and MDMs phagocytose myelin debris. I hypothesize therefore that microglia and MDMs phagocytose myelin debris to differing extents in an experimental model of MS. I induced focal demyelination by intraspinal injection of LPC transgenic mice (MicroTdT). MicroTdT flurorescently tag microglia, which allows differentiation from MDMs. The experimental endpoints were peak (3 days) and end (7 days) of phagocytosis. To compare microglia and MDMs phagocytic capacities, I measured microglial and MDM densities as well as volumes of the engulfed myelin debris. I found that microglia and MDMs have similar densities at 3 days, but microglia expanded to monopolize the LPC lesion by 7 days. Still, microglia and MDMs phagocytose myelin debris equally at 3 and 7 days. To understand how myelin debris clearance proceeds in the absence of microglia, I ablated microglia by genetically inserting the diphtheria toxin (DT) receptor into microglia and treating these mice and controls with DT. I found that MDMs compensate for microglial loss by phagocytosing more myelin debris, with no slowing of myelin debris clearance. Microglia and MDMs jointly phagocytose myelin debris. Future work will characterize the transcriptomes of phagocytosing microglia and MDMs. Understanding phagocytic mechanisms will provide targets to ultimately boost remyelination.

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2-C-179: Amyloid-beta oligomers induce changes in spectral activity during slow wave sleep in rats

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Synapse loss and ensuing neuronal death are the best predictors of memory deficits in Alzheimer's disease (AD). Hippocampus-dependant memory is the first type of memory that is affected in the disease because of the neurodegenerative process that takes place in the hippocampus of early AD patients. There is mounting evidence from recent studies that soluble low-molecular-weight amyloid-beta oligomers (Aβo) are the most neurotoxic species and that their presence correlate tightly with memory deficits. It is also well-established that sleep loss impairs the function of the hippocampus; and that sleep alterations are among the first clinical symptoms observed in AD. Moreover, the specific effects of Aβo on sleep are poorly understood. The main objective of this project was to determine the impact of soluble Aβo-induced neurodegeneration on sleep architecture and electroencephalographic (EEG) activity in rats. Chronic hippocampal of Aβo were performed in rats and combined to EEG measurements to assess alterations in sleep variables. Six days of Aβo injections in the hippocampus did not significantly changed time spent in wakefulness, slow wave sleep (SWS) or rapid eye movement (REM) sleep. However, we found a decrease in spectral power in theta (4-8Hz), alpha (8-12Hz), beta (12.5-30Hz) and low-gamma (30-60Hz) frequencies during SWS. EEG spectral analyses will be investigated across the six days of injection to determine how the progression of Aβo pathology affects sleep and whether it associates with the progressive increase in hippocampal neuroinflammation.

2-C-180: Neurodevelopmental impact of aberrant calcium mobilization in bipolar disorder patient-derived iPSC-neural progenitor cells

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Bipolar disorder (BD) is characterized by alternating cases of depression and mania. Although deviations in neurodevelopment are suspected to contribute to the pathophysiology of BD, the precise molecular underpinnings remain unknown. In cells, calcium plays an influential role in development via signalling cascades. As such, calcium accumulates in the endoplasmic reticulum (ER) from where it can be rapidly released in response to a second messenger. Calcium levels are, therefore, tightly regulated through store-operated calcium entry (SOCE)--a mechanism that promotes calcium influx through ORAI channels when the ER is depleted. Recently, we found striking evidence of aberrant SOCE activity in BD patient-derived induced pluripotent stem cells (iPSCs) differentiated into neural progenitor cells (NPCs) in comparison to iPSC-NPCs derived from healthy control individuals. This led us to discover unsuspected cellular phenotypes. Here, we first summarize calcium imaging data revealing the sharp difference in SOCE between BD patient-derived and control iPSC-NPCs. Second, we show that lower SOCE activity in BD cells correlates with reduced STIM/Orai puncta formation. Third, we reveal decreased proliferation in BD-derived progenitors, which we then connect to a premature neuronal differentiation phenotype affecting migration. Finally, we support this dysregulated

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development with cerebral organoid modelling. Together, our findings suggest a contribution of SOCE to BD through dysregulation in the neurodevelopment of NPCs.

2-C-181: Recovery of the glutamatergic descending drive from the gigantocellular reticular nucleus after spinal cord injury in mice

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Following spinal cord injury (SCI), the projections from higher centers are severed, including glutamatergic reticulospinal pathways arising from the gigantocellular reticular nucleus (Gi). Previous studies have shown anatomical plasticity of these reticulospinal pathways after incomplete SCI, however, little is known about their functional plasticity. Using optogenetic tools, kinematics, and electromyographic (EMG) recordings in VGluT2-cre mice, we investigated changes in motor efficacy of glutamatergic Gi neurons following a unilateral SCI. We recorded EMG activity of the ankle flexor Tibialis anterior (TA) and extensor Gastrocnemius lateralis (GL). Short pulses (10 ms) of photostimulations were delivered during treadmill locomotion to probe the ability of the Gi to modify the ongoing locomotor pattern. Before SCI, photostimulations of the Gi increased activity in muscles during their relaxed phase. After SCI, the excitatory response during locomotion was depressed in the ipsilesional and to a lesser extent in the contralesional TA and GL. Eventually, motor efficacy recovered in the left and right TA and GL. Changes in locomotor performances and motor responses were positively correlated in ipsilesional flexor and extensor muscles, while there were not in contralesional hindlimb muscles. Conditioning glutamatergic Gi neurons also improved spontaneous recovery during voluntary locomotion. In summary, glutamatergic Gi neurons were involved in motor recovery after SCI, thus suggesting that they could be a neurological target to treat patients living with SCI.

2-C-182: Naked mole-rat brain mitochondria tolerate in vitro ischemia

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Naked mole-rats (NMRs; Heterocephalus glaber) are among the most hypoxia-tolerant mammals. If and how these organelles tolerate ischemia and how ischemic stress impacts mitochondrial energetics and redox regulation is unknown. We hypothesized that mitochondria fundamentally contribute to in vitro ischemia resistance in NMR brain. To test this, we treated NMR (1-2 years) and CD-1 mouse (14-16 weeks) brain sheets with an in vitro ischemic mimic and evaluated mitochondrial respiration capacity and redox regulation following 15- or 30-mins ischemia or ischemia/reperfusion (I/R). We did not observe differences between sexes (4 males and 4 females) for either species, so we pooled data from both sexes for statistical analysis. We found that, relative to mice, NMR brain largely retains mitochondrial function and redox balance post-ischemia and I/R. Specifically: i) ischemia reduced complex I and II -linked respiration ~50-70% post-ischemia in mice, versus ~20-40% in NMR brain, ii) NMR but not mouse brain maintained relatively steady respiration control ratios and robust mitochondrial membrane integrity, iii) electron leakage post-ischemia was lesser in NMR than mouse brain and NMR brain retained higher coupling efficiency, and iv) free radical generation during and following ischemia and I/R was lower from NMR brains than mice. Overall, these findings support the hypothesis that hypoxia-

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tolerant NMR brain is also ischemia-tolerant and suggest that NMRs may be a natural model of ischemia-tolerance in which to investigate evolutionarily derived solutions to ischemic pathology.

2-C-183: Vitamin D3 attenuates oxidative stress and rescues motor, neuromuscular coordination and spatial memory dysfunction in 3-nitropropionic acid induced mouse model of Huntington s disease

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Background: Huntington's disease (HD) is an autosomal progressive neurodegenerative disorder characterized by the degeneration of striatal neurons. In the present study, we used a neurotoxin namely, 3-nitropropionic acid (3-NP) to mimic neurobiological and clinical symptoms of HD. Objective: To explore neuroprotective effects of VD supplementation in HD. Methodology: For present study C57BL/6 male mice (3-4 months of age; n=8-15 animals per group) were divided into four different groups namely; Group I: Vehicle treated with sterile saline, Group II: animals were induced intraperitoneal (i.p) with 75mg/kg of 3-NP in three consecutive doses as described previously by Fernagut et al. Group III: animals injected i.p with only 500IU/kg of VD for 15 days and Group IV: 500IU/kg (12.5 µg/kg) of VD was given for 15 days through i.p to post 3-NP (75mg/kg) injected animals. Behavioral tests like locomotor activity, gait analysis, rotarod analysis, and morris water maze were carried out for a total period of 30 days. After 30 days, animals were decapitated and striatal tissues were isolated to check the mRNA expression of neurotrophins (nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and antioxidative enzymes (superoxide dismutase (SOD), glutathione peroxidase (Gpx) and catalase (Cat). Results: Our behavior and mRNA results reflect that post VD treatment to 3-NP animals (Group IV) significantly rescued spatial memory deficits, locomotion dysfunction and neuromuscular coordination when compared with 3-NP induced HD mice (Group II). Conclusion: Overall, our current study infers that VD may rescue striatal neuron degeneration in HD and changes in the expression of antioxidative enzymes corroborate with the antioxidative property of VD.

2-C-184: Behaviour characterization of the Q175/B6 Huntington's disease mouse model

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Q175/B6 is a knock-in mouse model of Huntington's disease, a neurodegenerative disorder characterized by chorea, loss of motor control and cognitive deficits. The primary site of neurodegeneration in HD is the striatum, a brain region important for motor learning. Studies have revealed motor and cognitive deficits in Q175 mice on the open field, accelerating rotarod and water T-maze tasks. This study aims to replicate these findings in Q175 mice while conducting more detailed analyses on the specific patterns of behaviour during these tests using the DeepLabCut tracking software and the new Behavioral Segmentation of Open Field in DeepLabCut (B-SOiD) machine learning program. 10-month-old Q175 mice engaged in less locomotion and sniffing behaviours and more grooming and rearing as compared to wild-type during the open field. HD mice also showed motor deficits on the rotarod, with a

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reduced latency to fall and a greater number of foot slips. In mice that used a striatum-dependent response learning strategy during training of the water T-maze, Q175 animals took significantly longer to reach the hidden platform during both training and reversal phases of the task. These findings reveal that Q175 mice show notable motor and cognitive deficits at 10 months of age, including reduced exploratory behaviour and potentially increased anxiety-like behaviours in the open field. Experiments with 3-month-old Q175 mice are also underway. Future studies that examine striatal signalling during performance of these tasks are needed for evaluation of potential therapeutic treatments in HD. Funding provided by the Canadian Institutes of Health Research Foundation grant (Fdn-143210).

2-C-185: Modeling the impact of genetic risk on microglia states and function

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Microglia, the brain's resident immune cells, are highly dynamic and reactive to environment and genetic challenges. Multiple microglia states are observed in mouse and human brain but how these states are created and what the functional consequences of these states are still unknown. Our goal is to develop a platform that enables predictive tracking and targeting of detrimental immune cell states in patients. To answer this question, we turned toward human iPSC-induced microglia (iMGL) and single cell transcriptomics. Single cell transcriptomics revealed the presence of multiple microglia states in vitro and multiple states are found when iMGLs are stimulated with different brain-relevant challenges, including apoptotic neurons, synaptosomes, myelin and amyloid. Moreover, alignment of these data using Liger (Welch et al. Cell 2019) shows these states are similar to the ones observed in human and mouse in vivo, revealing several disease associated states, including disease-associated microglia (DAM). We also observed changes in microglia states depending on the challenge and genetic background, therefore validating that our platform is recapitulating key aspects of microglia states and could be used to specifically identify causes and functions of specific states. Together, our data identified key elements causing the formation of DAM and how AD risk genes affect disease-associated states and functions. This work will open the door to the identification of modulators of DAM and highlight new therapeutics avenues of AD.

2-C-187: Deficient DNA repair following mild traumatic brain injury and its contribution to sex-specific outcomes

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Mild traumatic brain injury (mTBI) is a growing public health issue as its incidence rate continues to climb. Following mTBI, individuals exhibit various symptoms affecting wakefulness, mood, and cognition, with worse outcomes reported in women compared to men. Previous research examining pathological changes in humans with history of mTBI and mice models showed a downregulation in DNA repair genes and an upregulation in DNA damage. Breast cancer type I (BRCA1), involved in single and double-stranded DNA repair, was among these DNA repair genes reported to be significantly downregulated in humans with history of mTBI. Due to its involvement in repairing DNA damage induced by estrogen

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metabolites as well, this research investigated deficient DNA repair and its impact on outcomes post-mTBI with emphasis on BRCA1, and how it contributes to sex-specific outcomes. Using a mouseline with a heterozygous BRCA1 deletion (BRCA1-KD) and a closed-skull repeated mTBI model via controlled cortical impact, pathological and behavioural changes were examined following injury, at 1- and 6-weeks. In addition to showing increased levels of DNA damage, BRCA1-KD mice exhibited worse impairments to learning and memory post-mTBI compared to controls. These outcomes also appeared to be exacerbated in females compared to males. As mTBI impacts millions of individuals annually, studying mTBI in the context of sex is imperative. This work, supported through funding from CIHR, highlights deficient DNA repair as a contributing factor to both brain dysfunction and sex-specific outcomes post-mTBI.

2-C-188: Calcium handling in striatal neurons in Huntington disease

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Huntington disease (HD) is a monogenic disorder with autosomal dominant inheritance. In HD patients, neurons involved in motor function degenerate leading to motor & cognitive problems. Dysregulation of synaptic function & Ca2+ handling is common in many neurodegenerative diseases. One level of Ca2+ regulation is at the endoplasmic reticulum (ER), & this regulation is abnormal in HD. The ER is also suggested to be involved in nuclear Ca2+ signaling, & I hypothesize that this signaling pathway is altered in HD. Sigma-1 receptors (S1Rs) - proteins located on the ER - play an important role in Ca2+ regulation & thus gene transcription. Interestingly, activating S1Rs has been shown to normalize this Ca2+ handling & restore synaptic function in HD mouse models. The goal of this project is to determine the link between S1Rs, Ca2+ handling, Ca2+ dependent gene expression, & synaptic function to better understand the pathophysiological mechanisms of HD & to find new potential treatments. Cortico-striatal co-cultures & imaging techniques were used. Our data shows interesting contributions of different Ca2+ channels to nuclear Ca2+ signaling. Ca2+ imaging also suggests impairments in nuclear Ca2+ signaling in HD spiny projection neurons in co-cultures. Furthermore, Activin A, a protein whose expression is Ca2+ dependent, is decreased in HD culture media, & its overexpression normalizes aspects of synaptic function. This project will help us understand the complex pathogenesis of HD & elucidate the roles of key therapeutic targets toward developing disease-modifying treatments.

2-C-189: GABAA receptor positive allosteric modulation has symptomatic and disease modifying effects in a mouse model of chronic stress

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Chronic stress is a risk factor for anxiety and depression and all are linked to reduced cognitive performance and neuronal atrophy. In these, there is reduced number of GABAergic neurons, reduced GABA release and altered GABAA receptor (GABAAR) functioning. GABAARs contain α subunits that essentially dictate functional outcome: sedation with α1 subunit potentiation, anxiolytic effects with α2/α3 and cognition with α5.

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Common GABAergic drugs, like benzodiazepines, act at α1/2/3/5-GABAARs but have side effects (sedation, dependence) mixed with mild anxiolytic effects and no cognitive benefits. Therefore, a therapy designed to increase α2/3/5 activity while also devoid of α1 activity has significant clinical relevance and potential. We investigated two enantiomers separately, GL-I-54 and GL-II-73, as well as their combined use as a racemic mixture (termed GL-RM) because of the desirable positive allosteric modulation profile when combined (α2/3/5 and α5 respectively). Using the unpredictable chronic mild stress (UCMS) model in C57BL6 mice (50% female; N=48 per study), anxiolytic, anti-depressant and pro-cognitive effects of GL-RM were assessed after acute or chronic administration. GL-RM reduced stress induced anxiety-like phenotypes and overcame stress induced cognitive deficits. Golgi staining after chronic GL-RM found GL-RM rescued dendritic spine density after UCMS in the PFC and CA1. Results support the value of a therapy with a α2/3/5 GABAAR selective profile to overcome chronic stress-induced mood symptoms and cognitive deficits, and detriments in neuronal morphology.

2-C-190: Impact of alpha-synuclein aggregation on protein degradation systems and its implication in Parkinson's Disease pathogenesis

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Parkinson's Disease (PD) is the second most common neurodegenerative disease in the world. Characterized by motor and non-motor symptoms, PD is associated with the loss of dopaminergic neurons in the Subtantia Nigra (Kalia and Lang, 2015). One of the major pathological hallmarks of the disease is the aggregation of misfolded proteins called alpha-synuclein (α-syn), which will lead to the formation of cellular inclusion known as Lewy bodies (Spillantini et al., 1997). However, how these aggregates disturb neuronal homeostasis leading to neurodegeneration remains elusive. Several studies showed a correlation between alterations of the degradation systems (autophagic or proteasomal), implicated in the protein quality control, and a-syn aggregation (Lehtonen et al., 2019). It is then relevant to know how an alteration of the degradation systems is involved in the pathogenesis of PD. To this purpose, our group recently created a new cellular model in which we control optogenetically and observe in real-time the aggregation of a-syn. This system called the LIPA (Light-Inducible Protein Aggregation) system nicely mimics key features of Lewy bodies (Bérard et al., under review). Using this cellular model, we were able to observe for the first time the effect of LIPA-induced aggregates on the proteasome and autophagy systems in living cells by using specific markers (Menéndez-Benito et al., 2005). Moreover, we also get interested in the inhibition of these systems and the effect on the aggregation. Taken together our observations reveal the impact of autophagy and proteasome dysfunctions in PD pathogenesis.

2-C-191: Exploration of the pro-angiogenic potential of pericytes in the repair of neurovascular unity following cerebrovascular accidents

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Stroke is one of the leading causes of death and disability in the world. Unfortunately, there is still no effective therapy to treat the disease. Therapeutic angiogenesis using potent pro-

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angiogenic agents has already been shown to provide therapeutic benefits. However, the use of such agents is a double-edged strategy because of the increased risk of exacerbation of vascular leakage. Pericytes are specialized mural cells that play a key role in stabilizing the angiogenic vasculature and possess plastic properties, as they are able to differentiate into endothelial cells by reprogramming. Because of their angiogenic and plastic properties, pericytes are an attractive target for developing new interventions to promote neurovascular repair after stroke. Using novel pharmacological and genetic approaches to target pericytes, our results indicate that a recently discovered platelet-derived growth factor, isoform D (PDGF-D), plays an important role in promoting pericyte plasticity contributing notably to a decrease in brain atrophy and a reduction in motor impairment. Furthermore, our data demonstrate that ex vivo pre-conditioned pericytes transplanted intra-nasally migrate to the lesion site and promote its vascularization, which leads to the regression of damage. The overall results therefore suggest that pericytes are an interesting target and a new tool for the development of new therapies against stroke

2-C-192: Perineuronal nets in the ventromedial prefrontal cortex of depressed suicides with a history of child abuse

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Background: Experiencing child abuse (CA) is considered as one of the strongest predictors of depression and suicide. Childhood and adolescence are characterized by critical periods (CP) of heightened cerebral plasticity, in which neural circuits can be more easily modified by experience. The closure of these CP is driven by the development of perineuronal nets (PNNs) around certain neurons in the brain. We hypothesize that CA occurring during these CP alters the recruitment and maintenance of PNNs in brain regions involved in emotional regulation. Methods: Well-characterized brain samples of ventromedial prefrontal cortex (vmPFC) from adult depressed suicides with or without a history of CA and matched controls were provided by the Douglas-Bell Canada Brain Bank. Immunofluorescent staining was performed with different combinations of cellular markers (PV, NeuN, Westeria Floribunda Lectin). Fluorescent in situ hybridization (RNAScope®) was performed to identify the phenotype of neurons enwrapped by PNNs. Whole slide and confocal images were analyzed using QuPath and FIJI. Results: As previously reported, PNNs were found to be covering PV+ interneurons and, to a lesser extent, pyramidal neurons (SLC17A7+). CA was found to be associated with higher densities, intensity and coverage of PNNs in the lower layers of the vmPFC. Conclusions: These results suggest that a history CA has a lasting impact on vmPFC circuitry. This may represent a mechanism through which early-life adversity increases vulnerability to psychopathologies and suicide. Experiments are under way to determine the mechanisms underlying this phenomenon, namely through an examination of proximal microglia, which have been shown to be implicated in the regulation and maintenance of PNNs in animal models.

2-C-193: A history of child abuse associates with fatty acid dysregulation in the anterior cingulate cortex of depressed suicides

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A history of child abuse (CA) strongly increases the lifetime risk of suffering from major depression and predicts an unfavorable course for the illness. Severe CA has been specifically associated with a widespread, robust, and lasting inhibition of oligodendrocyte function, coupled with impaired myelination of small caliber axons in white matter of the human anterior cingulate cortex (ACC). Given that myelin is extremely lipid-rich, one possible explanation for this finding could be a disruption of the lipid profile that composes the myelin sheath. Furthermore, the composition of fatty acids (FA) in myelin phospholipids has been demonstrated to influence its stability and permeability. Therefore, the objective of this study was to quantify and compare FA concentrations in postmortem ACC white matter in the choline glycerophospholipid pool (ChoGpl), a key myelin phospholipid pool, between adult depressed suicides with a history of CA matched depressed suicides without CA and healthy non-psychiatric controls. Total lipids were extracted according to the Folch method and lipids were separated into respective classes using thin-layer chromatography. FA methyl esters from the ChoGpl fraction were quantified using gas chromatography. Our analysis revealed significant differences in FA concentrations between groups, primarily involving the FAs in the arachidonic acid synthesis pathway, which is further corroborated with ACC RNA-sequencing data. Furthermore, the concentration of most FAs was found to decrease with age. These findings are the first to associate a history of early-life adversity with ChoGpl dysregulation in the human brain.

2-C-194: Physiological and Pathological transients in temporal lobe Epilepsy patients during intracranial recordings

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Interictal epileptiform discharges (IEDs) and Sharp Wave ripples (SWR) are pathological and physiological events in patients with temporal lobe epilepsy. Although these two events may display similar temporal frequency patterns, they carry different energy in different frequency bands. We study a group of epilepsy patients with medically resistant epilepsy (MRE) at the Lawson Research Center at UWO, implanted with SEEG depth electrodes (DE) to identify interictal abnormalities IEDs and differentiate them from SWRs using a new algorithm. The data were cleaned, denoised, montaged and segmented, such as sleep intervals and observed Ictals. The signal waveform and its power were extracted symmetrically in non-overlapping intervals of 500 milliseconds for event detection. Each waveform's power across all detected spikes was computed and clustered based on their energy distributions. The recordings included more than 720 hours of extracellular recordings from three patients with 450 hours of non-sleep data extracted from four hippocampus electrodes anterior and posterior hippocampus. Results indicate that IEDs carrying the largest power in the bands [30-45] Hz, SWR, on the other hand, are distributed between and [25-40] and [90-110] Hz. Our algorithm detected and successfully distinguished IED from SWRs based on their carrying energy during non-sleep periods. The waveforms' energy is more significant in

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sleep than awake (non-ictal) periods, and was this characteristic was used as an informative feature to cluster these two events.

2-C-195: Neurovascular study of the human umbilical cord from newborns exposed to cocaine during pregnancy

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Substance abuse during pregnancy is a critical public health concern associated with harmful maternal, fetal consequences and developmental disorders. Cocaine is one of the most common drugs involved in prenatal exposure, it is a sympathomimetic drug that induces vasoconstriction. We recently confirmed the presence of sympathetic fibers around blood vessels of human umbilical cords (UCs) from healthy newborns. It is unknown whether UCs innervation could be altered in pregnancies of cocaine users, and thus compromise maternal-filial blood flow. We evaluated the UCs innervation from newborns prenatally exposed to cocaine and compared it with healthy newborns. Immunohistochemical assays with anti-PGP9.5 and anti-TH identified a subpopulation of newborns from cocaine pregnant users with increased IR-PGP and -TH area surrounding the umbilical arteries. Reduced UCs arterial diameter was also found. Together, our results support the idea that direct vasoconstrictor effects on the umbilical vessels could take part in different conditions such as intrauterine-growth restriction, prematurity, low-birth-weight and subsequent developmental alterations. Ongoing investigations seek correlations between cocaine-induced increase in periarterial innervation and the clinical manifestations in newborns of cocaine users. Risk factors such as poly-consumption, gestational age and nutritional status are being evaluated. The establishment of associations between neurobiological and clinical variables will help us to understand the relationship between developmental disorders and prenatal drug use.

2-C-196: Investigating regional lipid expression profiles in post-mortem Alzheimer's disease brain tissue using MALDI-IMS

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Alzheimer's disease (AD) is a debilitating and progressive neurodegenerative condition that accounts for the vast majority of dementia diagnoses annually. Several brain regions have been implicated in the neuropathology of AD although the mechanisms of AD progression are poorly understood. The majority of pathological studies have focused on proteins, whereas perturbations in lipid expression within the AD brain are relatively under described. Lipids are the primary structural component of cell membranes, key players in neuroprotective and apoptotic pathways; and can even stimulate or inhibit transmembrane protein pumps. Profiling lipid expression may prove critical to understanding the complex underlying neurodegenerative mechanisms that comprise AD. Previously, detection of lipids in AD brain tissue has been limited by a lack of analytical imaging techniques capable of detecting complex lipid species and a need for fresh flash frozen tissue for mass spectrometry analysis. In this study we utilize a protocol developed in our lab to profile lipid

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expression in situ using matrix-assisted laser desorption/ionization imaging mass spectrometry (MALDI-IMS). For the first time, we present the lipid profile of several neuroanatomical regions critically implicated in AD pathology including the entorhinal cortex, nucleus basalis of Meynert, hippocampus, periventricular white matter and subcortical U-fibres in post-mortem AD and non-AD brains. This data will support an ongoing effort to better understand the underlying role of lipid dysregulation in AD pathogenesis.

2-C-197: Transcriptional assessment of genes structures in the human brain of men and women with major depressive disorder and their associations with the sex-specific symptomatic profiles

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Background: Major depressive disorder (MDD) is a leading cause of disability worldwide. Despite its societal importance, addressing this issue has not been successful yet, owing to the heterogeneity of the disease, with sexual dimorphism as the main source. Studies showed that MDD is also a disease of multi-brain regions. So far, no study has revealed the transcriptional organization of gene networks across brain regions and their associations with the clinical features of MDD in men and women. Methods: The RNAs extracted from 6 brain regions of post-mortem samples in men and women with and without MDD were sequenced. We used gene network approaches to map the transcriptional gene organizations across brain regions and associated those with symptomatic profiles in both sexes. We combined these approaches with conventional gene differential expression, gene ontology, and RRHO analysis to provide a thorough description of transcriptional profiles associated with the expression of specific symptoms. Results: Transcriptional signature patterns across brain regions are Sex-specific. We also identified a series of gene clusters, relevant to the expression of MDD in all the brain regions, including the ventromedial prefrontal cortex. In addition, while this brain region is associated with agitation and cognitive deficit in women, it is associated with loss/gain of appetite in men. Conclusion: Our findings revealed that MDD in men and women arises from the actions of similar clusters of genes, sharing cellular and biological pathways, but organized differently across brain regions in each sex. Moreover, the association of Clinical manifestation of MDD with modules in particular brain regions seems to be sex-specific.

2-C-198: The contribution of heterogeneous nuclear ribonucleoprotein A1 to oligodendrocyte biology using in vivo and in vitro models of multiple sclerosis

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Oligodendrocyte (OL) dysfunction and demyelination are crucial pathological features of multiple sclerosis (MS), but their underlying mechanisms in MS remain elusive. Recently, our lab discovered the contribution of neuronal dysfunction of RNA binding proteins (RBPs) such as heterogeneous nuclear ribonucleoprotein A1 (A1) and stress granule (SG) formation to the pathogenesis of neurodegeneration in MS. Previous studies have shown that A1 is involved in the regulation of myelin-related gene expressions in OLs. However, the function of A1 in OL biology in MS remains to be explored. C57BL/6 female mice were immunized

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with MOG35-55 to induce experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Immunohistochemistry staining was used to examine A1 dysfunction and cytoplasmic aggregation of G3BP, a marker for SG formation, in spinal cord OLs at the peak of EAE. siRNA knockdown against A1 was performed in an OL cell line to investigate its effects OL health. We found that EAE animals exhibited significant increases in A1 mislocalization and SG formation in OLs in spinal cords of EAE mice as compared to the naïve group. Furthermore, we observed that A1 colocalized within SGs in OLs in EAE mice. siRNA knockdown of A1 in OL cells resulted in increased cytotoxicity, decreased the number of junctions around the cells, and enhanced apoptosis and necroptosis. These data indicate that A1 is indispensable for OL health and function, which might involve in the pathogenesis of demyelination and neurodegeneration in MS patients.

2-C-199: Chd7 loss of function in zebrafish impairs GABAergic network development through MEK/ERK signalling: CHARGE syndrome and beyond.

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Mutations in the ATP-dependent chromatin remodeller chromodomain, helicase, DNA binding (CHD) 7 are the primary cause of CHARGE syndrome (CS) and have been associated with autism spectrum disorder (ASD). CHARGE is an acronym for the most characteristic features presented by patients: coloboma of the eye, heart defects, atresia chonae, retardation in growth and development, genital abnormalities, and ear defects. Although not included in the diagnostic criteria CS features often include neurological and behavioural problems such as hyperactivity, seizure, intellectual disability and autism. Little is known about the molecular mechanisms that underlie these neurological symptoms. Further, there is no known treatment yet either for patients with CS or for the neurological symptoms shared between CS and ASD. To investigate this, we generated a novel CRISPR/cas9 zebrafish chd7−/− model. We show that chd7 knockout zebrafish larvae exhibit a small head phenotype, defects in craniofacial cartilage development and display aberrant axonal network development. Further the chd7 mutants have less GABAergic neurons and exhibit a hyperactivity behavioural phenotype. Using an unbiased whole transcriptomic approach, we found that the GABAergic neuron defect was at least in part due to the downregulation of a CHD7 target gene, paqr3b and the subsequent upregulation of the MAPK/ERK signalling pathway, which is also dysregulated in CHD7 mutant human cells. Through a phenotype-based screen in chd7−/− zebrafish and C. elegans, we show that the small molecule ephedrine restores MAPK/ERK signalling and improves both GABAergic defects and behavioural anomalies. This work provides insight into the neuropathogenesis in CS and identifies a promising compound for further preclinical studies.

2-C-200: Mesencephalic astrocyte derived neurotrophic factor mediates lithium induced neuroprotection

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Although introduced 70 years ago, the monovalent cation lithium remains the 'gold standard' treatment for bipolar disorder; however, its therapeutic mechanism of action remains elusive. Accumulating data suggest that lithium's neuroprotective properties involve the modulation of ER-calcium binding proteins such as GRP78, coined the 'master regulator' of endoplasmic reticulum (ER) stress. Mesencephalic astrocyte derived neurotrophic factor (MANF) is an ER-resident protein with demonstrated neuroprotective capabilities against cellular insults through its direct interaction with GRP78. The purpose of this study was to determine whether lithium neuroprotection against ER stress is correlated with an increase in MANF and GRP78 through the AP-1 pathway. Mouse striatal cells were pretreated with either PBS, lithium or lithium + AP-1 inhibitor for 6 days before being exposed to thapsigargin, an inducer of cytotoxic ER-stress for 24 hours. Cell viability and gene expression were quantified using MTT assays and RT-qPCR, respectively. Our results show; (1) Protracted lithium treatment provides neuroprotection against thapsigargin-induced cell death. (2) Lithium neuroprotection was correlated with the elevated expression of MANF alongside GRP78 (3) Lithium neuroprotection was attenuated upon the addition of a potent AP-1 inhibitor, alongside the diminished increase in expression of MANF and GRP78. Taken together, these data suggest that lithium's neuroprotective mechanisms involve the modulation of pro-survival ER-resident proteins such as MANF through the AP-1 transcription factor. Knockout studies using the CRISPR-Cas9 system will determine the extent of MANF's involvement in lithium neuroprotection.

2-C-201: Syngap1 haploinsufficiency increases AMPA receptor-mediated synaptic transmission and thalamocortical input onto Parvalbumin-positive interneurons in mouse auditory cortex.

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Intellectual disability (ID) and autism spectrum disorder (ASD) are among the most common neurodevelopmental disorders observed in childhood and together with cognitive impairments, they often result in sensory processing deficits. SYNGAP1 haploinsufficiency-related intellectual disability (SYNGAP1-ID) is characterized by moderate to severe ID, generalized epilepsy and ASD. We have recently found that auditory sensory processing is altered in SYNGAP1-ID patients and Syngap1 haploinsufficient mice, however the underling cellular mechanisms are currently unknown. Here, we examined the cell-specific effects of Syngap1 haploinsufficiency on AMPA receptor (AMPAR)-mediated transmission onto Parvalbumin-positive, fast spiking GABAergic interneurons (PV cells) and pyramidal cells (PCs) from layer IV of mouse auditory cortex, using whole-cell voltage clamp recording in combination with electrical stimulation of thalamic fibers. We found that both the amplitude of AMPAR-mediated spontaneous EPSCs and the AMPAR-mediated evoked thalamocortical EPSC were increased only in PV cells from Syngap1 heterozygous mice compared to control littermates. Furthermore, the NMDA/AMPA ratio was affected in both cell types based on a different underlying mechanism, indeed AMPAR-mediated currents were increased in PV cells, while NMDAR-mediated currents were decreased in PCs. Taken together, these data suggest that, in Syngap1 heterozygous mice, thalamocortical recruitment of PV cells is enhanced; this may lead to altered feedforward inhibition onto PCs and contribute to abnormal auditory processing.

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2-C-202: SARS-CoV-2 spike protein induces brain pericyte immunoreactivity in absence of productive viral infection

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COVID-19 is a respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 pathogenesis causes vascular-mediated neurological disorders via still elusive mechanisms. SARS-CoV-2 infects host cells by binding to angiotensin-converting enzyme 2 (ACE2) that recognizes the viral spike (S) protein. Brain pericytes express ACE2 at the neurovascular interface, outlining their possible implication in microvasculature injury in COVID-19. Yet, pericyte responses to SARS-CoV-2 isn't clear. Here we report that ACE2 expression in human brain vascular pericytes is highly dynamic and is increased upon S protein stimulation. Pericytes exposed to S protein underwent phenotypic changes translated by increased expression of contractile and myofibrogenic proteins and an altered intracellular calcium dynamic. Furthermore, S protein induced lipid peroxidation, oxidative and nitrosative stress in pericytes as well as triggered an immune reaction, which was potentiated by hypoxia, a condition associated to vascular comorbidities. S protein exposure combined to hypoxia enhanced the production of pro-inflammatory cytokines. Finally, we found that S protein could reach the mouse brain via the intranasal route and that reactive ACE2-expressing pericytes are recruited to the damaged tissue undergoing fibrotic scarring in a mouse model of cerebral multifocal micro-occlusions. Our data demonstrate that the released S protein is sufficient to mediate pericyte immunoreactivity, which may contribute to microvasculature injury in absence of a productive viral infection.

2-C-203: Age-dependent alterations in electrophysiological properties of corticomotor neurons in C9orf72 heterozygous mice

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ALS is the most common motor neuron disease in humans, whereby upper and lower motor neurons degenerate, eventually resulting in death. A major hypothesis underlying the mechanistic origin of neurodegeneration in ALS postulates that cortical hyperexcitability facilitates cell death. Previous research has identified the G4C2 hexanucleotide repeat expansion in the C9orf72 gene as the most common genetic cause of ALS; however, little is known about the contribution of the C9orf72 gene to neuronal excitability in the primary motor cortex. Thus, using a C9orf72 heterozygous loss-of-function (C9-Het LOF) mouse model, we assessed the action potential firing frequency of corticomotor neurons using whole-cell patch-clamp recordings made from an acute brain slice preparation. We have found that prior to disease onset, the action potential firing frequency is significantly lower in the C9-Het LOF mice compared to wildtype mice. In contrast, after disease onset, the action potential firing frequency is significantly higher in the C9-Het LOF mice compared to wildtype mice. These results highlight disease-stage-specific changes in cortical excitability.

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Moreover, we have found no change in spontaneous excitatory postsynaptic current frequency or amplitude at either disease stage, suggesting unaltered excitatory network function. Further investigation into the local inhibitory circuitry will reveal essential information about the neurophysiological mechanisms underlying neurodegeneration in C9orf72 ALS patients, which could contribute to the development of future therapeutic strategies.

2-C-204: Pathological correlates of psychiatric phenotypes across brain regions in chronic traumatic encephalopathy

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[1]Boston University

BACKGROUND Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease with cognitive, behavioral, and psychiatric symptoms, with depression and suicidality present in a large proportion of CTE cases. Pathologically CTE is defined by a distinctive accumulation of hyperphophorylated tau (pTau) predominately involving the frontal and temporal cortices, medial temporal lobe, and brainstem. However, the association between pathology in particular brain regions and psychiatric CTE symptoms is unknown. METHODS AND RESULTS Human postmortem brains from CTE cases and controls were obtained from the VA-BU-CLF Brain Bank. Trained neuropathologists examined each brain for gross and microscopic pathology, and provided semi-quantitative assessments. Regions of interest (including frontal, temporal, limbic, and brainstem structures) were sectioned and stained for pathological markers of interest (e.g. pTau, β-amyloid, α-synuclein, pTDP43, etc). Stained slides were scanned and traced digitally, with staining quantified using a Leica Aperio system. Preliminary analyses suggest alterations in specific cortical, limbic, midbrain, and white matter structures may associate with depressive and suicidal features in CTE. In particular, cortical white matter loss as well as hippocampal and midbrain pathology were associated with psychiatric features. We have also found myelination and inflammation-associated changes in the anterior cingulate cortex of depressed CTE cases. CONCLUSIONS This investigation is the first to explore associations between neuropathology in particular brain regions and specific psychiatric features in CTE. Preliminary results suggest neurodegenerative pathology, loss of white matter, neuroinflammation, and gliosis could underlie psychiatric phenotypes in CTE.

2-C-205: Biomarkers of reduced inhibition in human cortical microcircuit signals in depression

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Major depressive disorder (depression) involves different mechanisms and brain scales. Altered cortical inhibition is associated with treatment-resistant depression, and reduced dendritic inhibition by somatostatin-expressing (SST) interneurons is a key component of the pathology. Electroencephalography (EEG) is an important source of biomarkers for depression to improve diagnosis and inform personalized treatments. However, whether the effects of reduced SST inhibition on microcircuit activity have signatures detectible in EEG

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remains unknown. We used detailed models of human cortical layer 2/3 microcircuits with normal or reduced SST inhibition to simulate resting-state activity together with the EEG signals in health and depression. We show that the healthy microcircuit models had emergent properties that reproduced key features of resting-state EEG theta-alpha frequency bands. We found that simulated EEG from depression microcircuits showed a significant increase in theta rhythmic activity and increased broadband power. Neuronal spiking showed a spike preference of EEG peak phase, and did not differ between conditions. We also showed using a realistic head model that the EEG signal biomarkers were mostly localized. Our study thus used detailed computational models to identify EEG biomarkers of reduced SST inhibition in cortical microcircuits in depression, which may serve to improve the diagnosis and stratification of depression subtypes, and in monitoring the effects of pharmacological modulation for treating depression.

2-C-206: Impaired hippocampal plasticity associated with loss of Christianson syndrome protein Slc9a6/Nhe6 is ameliorated by 7,8-dihydroxyflavone

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Proper maintenance of vesicular pH is a critical determinant of organellar function, particularly with regards to endocytic trafficking. Accordingly, mutations in the SLC9A6 gene encoding endosomal pH regulator Na+/H+ exchanger isoform 6 (NHE6), can result in severe diseases such as Christianson syndrome (CS), an increasingly prevalent form of X-linked intellectual disability. Unfortunately, little is presently known of how ablation of NHE6 function perturbs synaptic plasticity, such as long-term potentiation (LTP), to result in the severe cognitive impairments associated with CS. To address this, we generated a novel line of Nhe6 knock-out (KO) expressing fluorescent labeling within hippocampal neurons to assess synaptic structure, function, and learning mechanisms. In Nhe6 KO hippocampi, we uncovered significant reductions in mature dendritic spines along CA1 pyramidal neuronal dendrites, levels of the AMPA receptor (AMPAR) subunit GluA2, and AMPAR-mediated neurotransmission. In response to LTP stimulation, Nhe6 KO hippocampal neurons showed abnormal functional potentiation arising from a failure to upregulate surface GluA2 and phosphorylation of the AMPAR subunit GluA1 at the S845 site. In addition, spines along the dendrites of Nhe6 KO neurons were excessively motile, and larger KO spines failed to enlarge after LTP. Intriguingly, activated levels of tropomyosin receptor kinase B (TrkB) have previously been reported to be downregulated in Nhe6 KO hippocampi. As such, we sought to restore these deficits using the TrkB agonist 7,8-dihydroxyflavone (7,8-DHF), which restored deficits in spine density and functional and structural remodeling after LTP induction in Nhe6 KO hippocampal neurons.

2-C-207: Investigating the role of multifocal cerebral micro-occlusions in modulating Alzheimer's disease pathobiology

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Cerebral microangiopathies occur in an important proportion of Alzheimer's disease (AD) patients. Interestingly, cerebral micro-occlusions (CMO), which are caused by the

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obstruction of small penetrating arterioles, constitute the majority of cases. CMO provoke cerebral blood flow abnormalities and small ischemic lesions, which are jointly implicated in the etiology of AD. Accumulation of these microinfarctions overtime contributes to the neurodegenerative cascade observed in AD. Nevertheless, the underlying cellular and molecular mechanisms that link CMO to the pathobiology of AD remain unclear. In this project, we postulate that microinfarctions associated to CMO influence the neurodegenerative cascade via regulation of the inflammatory response leading to AD pathology modulation. Using a novel mouse model of CMO combined with various molecular, cellular, imaging and neurobehavioral approaches, we evaluated the repercussion of microinfarctions on AD dependently upon biological sex. Our findings indicate that CMO promotes early memory deficits and disinhibition in males whereas in females those deficits are transitory. These changes were accompanied by a reduction in the plaque number and volume without affecting amyloid-ß soluble forms. Notably, CMO triggers early cell degeneration accompanied by a robust microglial and astrocytic activation and the recruitment of peripheral immune cells. Our preliminary findings suggest that CMO causes early cognitive and executive impairments in AD through regulation of the inflammatory response independently upon amyloid pathology.

2-C-208: Rathletes do not give you wings: How paternal exercise, caffeine, and/or alcohol affects offspring pathophysiology and behaviour following repetitive mild traumatic brain injury (RmTBI)

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Only recently has the scope of parental research expanded beyond maternal contributions to include the paternal sphere. Epidemiological studies have suggested that paternal stress, nutrition, and alcohol consumption, all impact neurobiological and behavioural characteristics in offspring. Given their high prevalence and comorbid use, a severely understudied domain in paternal research includes caffeine, alcohol use, and exercise. In this experiment, sires received seven weeks of regular tap water (placebo) or caffeine and/or ethanol (drug) and were housed in regular static cages (no ex) or cages with running wheels attached (ex). Beginning at P40, offspring were administered RmTBIs or sham injuries, followed by a behavioural test battery designed to assess post concussive symptomology. Post-mortem qRT-PCR was used to assess gene expression in the prefrontal cortex (PFC) and nucleus accumbens (NAc). Paternal experience did not improve or exacerbate RmTBI outcomes. However, female and male offspring displayed unique responses to RmTBI and paternal experience, resulting in sex-dependent changes in physical, behavioural, and molecular outcomes. Injury and paternal exercise drove significant changes in female offspring, whereas male offspring were affected by paternal exercise and drug treatment. Our findings add valuable insight into paternal experience and epigenetic inheritance in offspring. While not directly exacerbating or improving recovery from RmTBI, paternal experience affected male and female offspring in a sexually dimorphic manner.

2-C-209: COVID-19 is associated with a broad spectrum of neurological disease

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Background Coronavirus disease 2019 (COVID-19) frequently disturbs the nervous system. However, COVID-19's neurological disease requires a detailed characterization. Furthermore, we do not know what predicts poor neurological outcomes in patients. Previous reports have linked neurological disturbances to COVID-19's increased mortality. Here, we describe the clinical alterations in COVID-19 patients presenting with neurological manifestations and correlate neurological outcomes with disease severity. Methods We retrospectively analyzed clinical, neurological, neuroimaging (CT or MRI scans) and cerebrospinal fluid (CSF) laboratory data from 33 confirmed COVID-19 hospitalized Brazilian patients subjected to CSF sampling as clinically indicated. Findings COVID-19 was associated with a broad spectrum of neurological diseases in mild and severe cases. Headache was the only symptom associated with mild disease. In a bivariate analysis, severe patients had an 18-fold increased risk of presenting neuroimaging alterations. CSF findings do not differ in severe and mild cases. Only four patients presented increased CSF white blood cell counts. CSF levels were high for protein in 12 patients and glucose in six patients. Interpretation These findings strengthen the notion that COVID-19-induced neurological disease is heterogeneous and manifests regardless of patient state. It will be most important to determine the time course of neurological disease and whether it is permanent or alleviated over time so that COVID-19 patients with neurological alterations can be adequately treated.

2-C-210: The role of palmitoylating enzyme, zDHHC9, in intellectual disability

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Loss-of-function variants in the human Zdhhc9 gene are identified in 2% of patients diagnosed with X-linked intellectual disability. These patients exhibit striking reductions in white matter volume and altered microstructure of white matter tracts. To further understand the role of Zdhhc9 in the brain and to elucidate how disrupting Zdhhc9 function contributes to phenotypes observed in patients, we have characterized a Zdhhc9 knockout mouse line. We demonstrate that Zdhhc9 is enriched in oligodendrocytes and is approximately two-fold higher in the corpus callosum than in any other region of the mouse brain. Zdhhc9 knockout mice exhibit significant reduction in myelin/oligodendrocyte associated markers, as well as reductions in the palmitoylation of these proteins, suggesting palmitoylation of myelin proteins may be required for their stability. RNA sequencing of different brain regions from control and Zdhhc9 knockout mice demonstrate differential expression of oligodendrocyte marker genes, suggesting a larger population of immature oligodendrocytes and fewer mature oligodendrocytes in knockout brains. This work provides a new perspective into the role of Zdhhc9 in oligodendrocytes and provides evidence that palmitoylation contributes to the development of white matter.

2-C-211: CDK14 regulates alpha-Synuclein levels and toxicity

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Parkinson's Disease (PD) is a debilitating neurodegenerative disease pathologically characterized by the abnormal accumulation of the α-Synuclein (α-Syn) protein. Patients with multiplications of the α-Syn gene have familial PD, and animal models that overexpress α-Syn replicate several features of PD. Therefore, decreasing α-Syn levels may be a feasible approach to mitigate neurodegeneration. A genetic screen for modifiers of α-Syn levels identified CDK14, a brain-enriched kinase of largely unknown function as a robust regulator of α-Syn, whereby reducing CDK14 levels decreased the α-Syn load. Importantly, Cdk14-null mice display normal brain architecture, fertility, and viability. We tested the genetic reduction of CDK14 levels in two models of PD: mice injected with toxic α-Syn pre-formed fibrils and mice which overexpress human α-Syn. Our data suggest that decreasing CDK14 protein levels improves locomotion, grip strength, gut motility, and mouse well-being in the PD mouse models. Furthermore, reduction of CDK14 decreased insoluble α-Syn levels by 13% and increased soluble pSer129 α-Syn by 86% in α-Syn-overexpressing mice. Finally, we targeted CDK14 in vitro via pharmacological inhibition and observed robust reduction of α-Syn levels. Thus far, our results support the potential of CDK14 as a novel therapeutic target for PD. Future experiments will focus on optimizing in vitro dosage of the CDK14 inhibitor and studying its pharmacokinetic properties in vivo.

2-C-212: Compound C and JZL184-combination treatment promotes ischemia-activated pericyte reprogramming and differentiation

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Pericytes are perivascular cells involved in blood-brain barrier maintenance under physiological conditions. Following ischemia, pericytes can activate (a-pericytes) and reprogram into induced multipotent neural stem cells (i-NSCs). Our previous work showed that AMPK inhibitor compound C (CpdC) facilitated a-pericyte reprogramming into i-NSCs and monoacylglycerol lipase (Mgll) inhibitor JZL184 was able to promote NSC differentiation into neurons. We propose that sequential treatment with CpdC followed by JZL184 after ischemia could enhance a-pericyte reprogramming and differentiation to promote pericyte-derived neural regeneration and improve functional recovery. Stereotaxic injections of vasoconstrictors endothelin-1 and L-NAME into the sensorimotor cortex were performed on Tbx18-CreERT2/YFP-flx mice treated with tamoxifen pre-stroke to lineage trace Tbx18-YFP+ pericytes following focal cortical ischemic stroke. CpdC or vehicle was administered once daily for 5 days starting day 1 post-stroke. At 7 days post-stroke, CpdC group showed a higher proportion of Tbx18-YFP+ cells expressing nuclear Sox2, a marker of NSCs. When another cohort of mice initially treated with CpdC (or vehicle) was continued with JZL184 (or vehicle) treatment once every 2 days, CpdC+JZL184-treated group showed a higher proportion of Tbx18-YFP+ cells expressing the neuroblast/immature neuron marker DCX compared to vehicle-treated group 14 days post-stroke. CpdC+JZL184-treated mice also showed greater recovery of spontaneous forelimb motor deficit measured by cylinder test. These findings provide early evidence that this combination drug treatment has the potential to promote local neural regeneration from ischemia-activated pericytes and can inform future regenerative therapies for ischemic stroke.

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2-C-213: Functional brain networks alterations in bipolar disorder: evidence from EEG and Graph theoretical analysis

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Bipolar disorder (BD) is characterized by different functional changes in the brain. BD adversely affects human behavior, speech, and cognition. However, the neural basis of BD is still poorly understood. In this study, we apply graph theory analysis to compare functional brain networks features between BD and normal control individuals. Twenty-one individuals in each BD and control groups were participated in this study. Resting state electroencephalography (EEG) was recorded in the resting state condition for each participant in both groups. Then functional brain networks (derived from calculation of lagged coherence between source localized current densities) were compared between groups. Using graph theoretical analysis, we found that BD group exhibited significant reduction in clustering coefficient, global efficiency, largest eigenvalue, and the second smallest eigenvalue in the theta (4-8 Hz) and alpha bands (8-12 Hz). These results suggest that BD is associated with alterations in segregation, integration, synchronizability and robustness of functional brain networks. According to these results, BD group exhibited reduced neural information processing in global brain network scales and specific modules that can be associated with cognitive/behavioral deficits in BD.

2-C-214: Upregulated astrocyte purinergic signalling increases neurite extension and neuronal activity in a mouse model of Fragile X syndrome

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Disordered communication between neurons and glia underlies many neurological symptoms of Fragile X syndrome (FXS), the most common heritable form of autism. Reciprocal crosstalk between neurons and glia can occur through the purinergic signalling pathway, which utilizes UTP, ATP, and their metabolites as predominantly excitatory signalling molecules. We recently identified novel FXS cortical astrocyte purinergic signalling upregulations in an Fmr1-/- mouse model of FXS, including elevated expression of metabotropic P2Y2 and P2Y6 purinergic receptors, increased intracellular calcium release following P2Y activation, and dysregulated intracellular levels of purinergic signalling molecules. Given these dysregulations, we also aimed to determine how elevated astrocyte purinergic signalling impacts neuronal morphology and activity. In wildtype and Fmr1-/- neurons grown in wildtype astrocyte-conditioned media, UTP treatment increased neurite outgrowth to levels comparable with control-treated neurons grown in Fmr1-/- astrocyte media, suggesting that elevated purinergic secretions may drive neurite extension through P2Y receptors. We also observed elevated neuronal activity in Fmr1-/- astrocyte-neuron co-cultures plated on microelectrode arrays, which was normalized to wildtype levels through chronic application of selective P2Y2 antagonist AR-C 118925XX. Astrocyte purinergic signalling therefore appears to influence both Fmr1-/- neuronal morphology and firing, and selective purinergic antagonism may warrant further investigation in the search for innovative FXS treatments.

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2-C-215: Profiling EV microRNAs from degenerating neurons to identify biomarkers for multiple sclerosis

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Multiple sclerosis (MS) is primarily characterized by demyelination within the central nervous system; however, the sustained clinical deficits associated with progressive forms of the disease are correlated with neuronal degeneration and death. Several mechanisms occurring within the MS lesion environment have been associated with axonal damage, including oxidative stress, hypoxic stress and glutamate excitotoxicity. Currently, there are no therapies preventing the neurodegeneration underlying chronic disability in progressive MS. Accordingly, biomarkers of neuronal damage that may suggest novel therapeutic targets and serve as prognostic indicators of disease progression are of great need. microRNAs (miRNA) are small, non-coding RNA molecules that inhibit translation of messenger RNA. They are often secreted from cells within extracellular vesicles (EVs), which are highly stable in circulation and abundant in human blood samples. Here, we use a reductionist in vitro culture system to profile miRNA expression in EVs released from human iPSC-derived neurons challenged with MS-relevant stimuli. We show that iPSC-derived neurons degenerate upon exposure to toxic stimuli and that EV miRNAs can be reproducibly obtained from degenerating neurons for sequencing. We aim to identify regulated EV miRNAs in our in vitro assays which can then be compared to neuronally-derived EVs isolated from MS patient plasma. We hope to identify a conserved miRNA signature that can be used to monitor neurodegeneration and disease progression in MS, while defining new neuroprotective strategies.

2-C-216: Transcriptomics analysis in a mouse model of spinocerebellar ataxia type 6 (SCA6)

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Spinocerebellar ataxia type 6 (SCA6) is a rare, late-onset disease, characterized by progressive ataxia and cerebellar degeneration. It is caused by an expansion of the CAG triplet repeat in the gene CACNA1A encoding (1) the α1 subunit of the P/Q-type calcium channel and (2) the transcription factor α1ACT. How this expansion causes SCA6 pathophysiology is incompletely understood. We use a humanized mouse model with an expanded triplet repeat (SCA684Q/84Q) that recapitulates the late-onset and progressive nature of the human disease to study its pathophysiology. Since one of the CACNA1A gene products is a transcription factor, we wondered if the transcriptome might be altered in SCA6. To screen for novel transcriptomic changes in an unbiased manner, we performed RNA sequencing on SCA684Q/84Q and control animals at 7 months, the age when motor deficit emerges, and sequenced mRNA from the cerebellar vermis, the brain region where prominent pathophysiological changes have been observed. Differential expression analysis on the sequence reads identified over 500 significant differentially expressed genes in SCA6 compared to wildtype controls, with roughly half up- and half down-regulated. We next performed pathway enrichment analysis to gain insights into the biological mechanisms represented by these genes. We identified both previously-characterized pathways, such as

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ion channels, as well as previously-uncharacterized pathways, such as mitochondrial proteins. Work is ongoing to explore whether these newly-identified pathways contribute to SCA6 pathophysiology.

2-C-217: Characterizing the window of vulnerability in a mouse model of mild traumatic brain injury

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Following a mild traumatic brain injury (mTBI), there is a window of vulnerability during which a subsequent mTBI may cause exacerbated neurological impairment. Current clinical guidelines cannot accurately assess the window's duration and may place patients at unnecessary risk of developing severe outcomes following a repeat injury. To investigate this phenomenon, we aimed to establish a closed-scalp, tip-driven mouse model of mTBI in which the window of vulnerability is well-defined. Male and female C57BL/6 mice received two sham operations, one sham operation and one mTBI, or two mTBIs separated by 1, 7, or 14 days. One week after the second operation, mice were assessed in the Y-maze spontaneous alternation task and visual cliff test to measure deficits in short-term memory and visual perception, respectively. The white matter integrity of each mouse's brain was assessed by silver staining in the corpus callosum and optic tract regions. Mice receiving two mTBIs did not differ in behavioural scores but showed exacerbated white matter damage relative to mice receiving one mTBI for all inter-injury intervals, indicating that the window does not resolve in our model within 14 days. Additionally, male mice receiving two mTBIs exhibited worsened white matter damage compared to female mice for all inter-injury intervals. Our results suggest that the window of vulnerability in mice may be longer than previously considered and indicate that male mice have enhanced vulnerability to multiple mTBIs compared to female mice.

D - Sensory and Motor Systems

2-D-218: Patients with a mild traumatic brain injury: what happens to their sense of smell in the acute phase ?

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Introduction: Olfactory dysfunction (OD) is a well-established consequence of traumatic brain injury (TBI). Most of the studies reported OD in patients with moderate and severe TBI in the acute phase. However, inconsistent results have been found on OD in patients with mild traumatic brain injury (mTBI). This study aims to investigate olfactory perception in patients with mTBI in the acute phase. Method: We measured olfactory capacities in 53 patients with mTBI between 2 and 4 weeks following their trauma and in 53 healthy controls (HC). More specifically, we administered a well-established olfactory test (Sniffin'Sticks) and we measured odor detection (yes/no paradigm) and odor perception of 4 common odorants (eucalyptol, benzaldehyde, parmesan cheese, geraniol), by using a computer controlled

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automated odor presentation device (olfactometer). Results: We did not observe any group difference in the Sniffin'Sticks test scores. However, compared to HC, mTBI patients showed more difficulty detecting odors (p= .001) and perceived them as more intense (p= .015). Furthermore, depending on the odorant (interaction odor * group: p= .001), mTBI patients perceived odors as less pleasant than HC. Conclusion: These findings show that patients with mTBI suffer from altered olfactory detection and perception from the first weeks following their trauma. However, well-established olfactory tests such as the Sniffin'Sticks test may not be sufficiently sensitive to these changes.

2-D-219: Serotonergic modulation of population coding

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Organisms have developed coding strategies that are optimized to best encode highly dynamic natural stimuli in order to survive. This process is thought to be mediated by neuromodulators such as serotonin. In the weakly electric fish Apteronotus leptorhynchus, serotonin has been shown to optimize neural and behavioral responses to stimuli associated to a specific social context. However, these results were based on single neuron recordings, whether and, if so, how serotonin optimizes coding at the population level remains unknown. Here, we investigated how serotonin modulates population coding of social stimuli using electrophysiological recordings. Preliminary results show that behavioral responses are associated with the presence of correlated activity across neural population and that release of serotonin led to increases in both signal and noise correlations, and increased the performance of an optimal linear decoder at reconstructing the detailed timecourse of the stimulus based on neural activities. As such, our results provide, for the first time, experimental evidence that serotonin optimizes coding of sensory social stimuli by a population of neurons.

2-D-220: Disrupted circadian clock function in the striatum affects dopamine-related motor responses

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Circadian clocks are ubiquitous throughout tissues and organs in mammals, forming a multioscillatory network that controls daily rhythms in physiology and behavior. A brain region expressing circadian clock genes is the striatum; a basal ganglia structure receiving dopaminergic input plays a major role in motor control. It is composed of distinct populations of medium spiny neurons (MSNs), either expressing Dopamine receptor D1 (DRD1) of the direct (stimulatory) or Dopamine receptor D2 (DRD2) of the indirect (inhibitory) pathway. Components of the dopamine signalling pathway and circadian clock genes mutually influence one other in striatal MSNs, which are key in the role of behaviorial control. Thus, we hypothesize that appropriate motor responses to a selective dopaminergic stimulation of either direct or indirect pathway depends on proper striatal clock function. Experiments were carried out on mice with a conditional knockout (KO) of the core clock gene Bmal1 from MSNs. Under baseline conditions, male and female Bmal1 KO mice display a hyperactive phenotype. To determine whether dopamine signaling was altered in the MSNs, mice were treated with a D1 and D2 receptor agonist and their locomotor activity were recorded in the

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context of the open field. KOs of both sexes display an attenuated response to the D1 agonist relative to controls, whereas the D2 agonist suppresses activity similarly in KO and control animals of both sexes. Data suggest that disrupted clock function in MSNs influences the locomotor outputs of the basal ganglia, particularly within the direct pathway.

2-D-221: 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 initiate and accelerate 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.

2-D-222: Sex differences in chloride homeostasis of c-fiber primary afferents in the spinal cord dorsal horn.

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Introduction: Intracellular Cl- concentration ([Cl-]i) is high in primary sensory neurons due to the activity of the Na+-K+-Cl- cotransporter 1 (NKCC1), causing greater Cl- accumulation than typically seen in CNS neurons. Consequently, central terminals of primary afferents in the spinal dorsal horn experience depolarization upon activation of GABAA receptors (GABAAR). Thus, regulation of [Cl-]i in these terminals may significantly affect transmitter release. Determining the exact [Cl-]i in C-fiber terminals is pivotal to understand sensory processing. Methods: To image [Cl-]i we used the genetically-encoded ratiometric Cl-sensor, superclomeleon, using 2-photon microscopy in acute spinal cord slices. Superclomeleon was virally transduced selectively in C-fibers in NaV1.8-cre mice. The GABAAR agonist and antagonist muscimol and bicuculline, as well as the NKCC1 antagonist

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bumetanide, were used to modulate [Cl-]i in afferent terminals in the dorsal horn. NKCC1 mRNA levels in the dorsal root ganglia was evaluated with RNAScope. Results: We found that [Cl-]i in C-fibers was significantly higher in males than females. Bumetanide significantly decreased [Cl-]i in males but not in females. Bicuculline did not significantly affect [Cl-]i in C-fibers indicating a minimal contribution of tonic GABAA signaling to [Cl-]i. NKCC1 mRNA was also significantly lower in females than males, consistent with the functional data. Conclusion: Presynaptic inhibition appears to be under distinct control by GABAergic inhibition between sexes, which should be taken into consideration in future studies.

2-D-223: Insights into neural characteristics that predict perineuronal net expression in brain circuitry

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Perineuronal nets (PNNs) are extracellular matrices that surround various types of neurons and are thought to restrict the plasticity of the neurons they surround. For example, the increased expression of PNNs around parvalbumin (PV) interneurons in sensory areas are thought to consolidate mechanisms of sensory processing. Given their effects on neural function, it is important to better understand the characteristics of neurons associated with PNNs (i.e., to predict which neurons will be surrounded by PNNs), as such neurons might be most important for adaptive brain functioning. Given the importance of PV to neural plasticity, we tested the hypothesis that PNNs were more likely to be associated with neurons with more intense PV expression. To this end, we analyzed PV intensity in PV neurons with or without PNNs in sensory and sensorimotor brain structures. We first examined this pattern in adult zebra finches, a songbird with discrete sensory and sensorimotor brain circuits for vocal learning and control. Consistent with our hypothesis, PV intensity was greater in PV neurons surrounded by PNNs than in PV neurons without PNNs in sensorimotor brain areas. We are currently extending these analyses across development, between sexes, and in other species (e.g., rodents) to assess the degree to which this pattern relates to developmental, sex, and species variation in behavioral plasticity.

2-D-224: Effector-specific spatial codes in dorsolateral prefrontal cortex during a head-unrestrained reach task.

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Dorsolateral prefrontal cortex (DLPFC) is associated with executive control and response selection, but the extent to which it is involved in effector-specific transformations is unclear. We addressed this question by recording single neurons from dorsolateral prefrontal cortex (DLPFC) while two trained monkeys performed a head-unrestrained reaching paradigm that allowed freely coordinated motion of gaze, head reaching in depth. Animals touched one of three central LEDs at waist level while maintaining gaze on a central fixation dot and were rewarded if they touched a target appearing at one of 15 locations in a 40° x 20° (visual angle) array. Preliminary analysis of 271 neurons in both monkeys showed an assortment of target/stimulus, gaze, pre-reach and reach-timed responses in DLPFC. We first tested for gaze, head, and hand gain fields during the different neuronal responses and found that 38%

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of the responses were gain modulated by initial hand position. A small fraction of neurons showed gain fields for initial eye position (4%), and for both initial eye and hand position (6%). After removing the gain field effects, we fitted the residual data against various spatial models and found that the visual response best encoded the target relative to space (Ts), whereas responses at gaze and hand onset showed a tendency towards coding hand displacement (dA). In addition, some (20%) neurons showed a preference for coding final head position or displacement. A more complete analysis will describe the complete coding and distribution of gaze, head, and reach signals in this region.

2-D-225: dI3 interneurons maintain hindlimb motor tone in mice following spinal cord injury

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The dI3 population of spinal cord interneurons (INs) is a group of excitatory INs that receive varied sensory afferent input and project to ipsilateral motoneurons. Prior experiments have discovered that the permanent silencing of dI3 INs has a minimal impact on locomotor function in intact animals, but substantially interferes with locomotor rehabilitation/recovery after spinal cord injury (SCI). To gain insight into how dI3 INs are involved with locomotor function and recovery, the inhibitory DREADD receptor (hM4Di) was expressed in dI3 INs using a hybrid line of transgenic mice (Isl1-Cre:Vglut2-Flp x FlexloxFlexFRT-hM4Di). Consistent with prior experiments, transient inhibition of hM4Di-expressing dI3 neurons with the DREADD agonist JHU37160 (0.5mg/kg) did not significantly impact locomotor function in intact animals. However, in T9-T10 SCI mice, transient silencing of dI3 INs resulted in a significant loss of flexor motor tone, demonstrated by a significant increase in the resting ankle joint angle (+43.9° ± 11.6°, n=7, t-test, p=0.0065). This coincided with decreased stepping and the qualitative appearance of hindlimb flaccidity during the treadmill locomotor task. Based on these results, dI3 INs appear to adopt a more significant role in hindlimb function after SCI, specifically the maintenance of basal motor tone in the absence of supraspinal input. Given that SCI patients often experience both hypotonia and spasticity (increased motor tone), these findings provide the impetus for targeting dI3 INs to modulate motor tone below the level of the lesion.

2-D-226: Exploring the interaction between function and organization in mouse visual cortex using a novel spatially integrated optogenetic system.

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[1]University of Montreal

Multiple studies have shown that mouse higher visual areas are involved in discrimination task through intricate functional properties and complex networks. However, it remains enigmatic how this highly connected network define specialized perceptual roles in extrastriate areas and how these interact in mouse behavior. Here we sought to study the connectivity and perceptual roles of these extrastriate areas using patterned optogenetic inactivation combined with mesoscopic calcium imaging. (A) Our first goal will be to develop a novel system of photostimulation using a the digital micromirror device (DMD), which uses mirrors to precisely shape a light beam into a large surface. Such innovative technology opens new doors in optogenetics as brain areas often have complex shape and are

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interconnected with remote areas. Validation on Channelrhodopsin-expressing mice showed robust local and long-range activations using the red calcium indicator jrGECO1a. Our second goal (B) is to implement this novel method of stimulation to our inactivation paradigm and assess how the inactivation of a whole extrastriate area impact the functional properties of adjacent areas and on feedback connections to the primary visual cortex using calcium imaging. Our final goal (C) is to study how perceptual learning is affected during spatially integrated optogenetic inactivation. Overall, studying visual perception require rigorous knowledge on the function and the organization of visual areas and this research will have the potential to bring new light unto this interaction.

2-D-227: Mechanisms for integrating allocentric and egocentric visual information for goal-directed movements: a neural network approach

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Allocentric (landmark-centered) and egocentric (eye-centered) visual information are optimally integrated for goal-directed movements. This process has been observed within the supplementary and frontal eye fields, but the underlying processes for this combination remain a puzzle, mainly due to inadequacy of current theoretical models to explain data at different levels (i.e., behavior, single neuron, and distributed network). Here, we propose a physiologically inspired neural network with two major components: First, a Convolutional Neural Network (CNN) is used to extract the allocentric information (target and landmark): We used repeated (2 layers) convolution, rectifications, and normalization followed by a feature pooling layer to extract allocentric information (target and landmark). Second, a Multi-Layer Perceptron network (MLP, 3 fully connected layers) is used to incrementally transform allocentric information into an integrated motor response. We added an additional layer to transform motor responses into final gaze positions. The network was trained on both idealized and actual monkey gaze behavior. MLP output units accurately simulated prefrontal motor responses (including open-ended response fields that shifted partially with the landmark) and their decoded output achieved good correspondence (MLP: R2 = 0.80) with actual gaze behavior (Bharmauria et al. Cerebral Cortex 2020). These results suggest that our framework works and provides a suitable tool to study the underlying mechanisms of allocentric and egocentric integration. Supported by a VISTA Program fellowship.

2-D-228: Functional network topography reveals dorsal-ventral cortical modules for visual feature memory, and lateralized modules that combine for transsaccadic integration

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Considerable regional evidence has accumulated for dorsal-ventral modularity in the visual system, but it is not clear how these modules function at the whole brain network level, or how these networks are influenced by naturally occurring saccades. We addressed these questions using graph theory analysis of fMRI data collected during a task where participants had to remember, then discriminate between two different object features. Seventeen participants judged whether a remembered object changed shape or orientation with or

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without an intervening saccade. BOLD activation from 50 cortical nodes was used to identify local and global network properties. A network modularity analysis revealed three sub-networks during fixation: a bilateral dorsal sub-network linking areas involved in visuospatial processing and two lateralized ventral sub-networks linking areas involved in object feature processing. Importantly, when horizontal saccades across the remembered object required visual comparisons between hemifields, the two lateralized ventral sub-networks became functionally integrated into a single bilateral sub-network. Comparisons of 'betweenness centrality' between conditions identified several significant hub regions in occipital, parietal, and frontal cortex involved in linking distant network nodes during saccades. These results provide support of a ventral and dorsal stream distinction in human perception and show how hemispheric sub-networks are modified to functionally integrate information across saccades.

2-D-229: Prey localization and population coding in the electrosensory system of Apteronotus leptorhynchus

Myriah Haggard[1], Maurice Chacron[1]

[1]McGill University

Animals continuously process sensory information in order to interact with the environment. Foraging requires this continuous sensory input, and a core sensory component is estimating the location of food relative to self. Depending on the animal, different sensory systems are involved in this estimation (i.e., visual, auditory, somatosensory, and electrosensory). The weakly electric fish, Apteronotus leptorhynchus, uses its electrosensory system to locate prey. Using simultaneous electrophysiological recordings of populations of neurons early in the electrosensory circuit, we are studying the precision with which the neural responses can be used to estimate prey location. Preliminary results indicate that even small numbers of neurons can locate prey with sufficient precision for capture. We hypothesize that topographically organized feedback enhances the sensitivity of the neurons to prey stimuli in order to facilitate localization, acting like a sensory searchlight. Therefore, we are pharmacologically inactivating feedback to test this hypothesis. Concurrently, we are studying the statistical properties of these neural populations (i.e., noise correlations), their impact on location estimates and how they change when feedback is blocked. Preliminary results show that noise correlations are detrimental to decoding location, but the spatial dependence of these correlations lessen the detrimental impact. Due to similarities across sensory systems, these studies of feedback and the statistics of population coding will advance our understanding of object localization in other sensory systems.

2-D-230: Sexual dimorphism in a neuronal mechanism of spinal hyperexcitability across rodent and human models of pathological pain

Annemarie Dedek[1], Jian Xu[2], Louis-Étienne Lorenzo[3], Antoine Godin[4], Chaya Kandegedara[1], Genevieve Glavina[5], Jeffrey Landrigan[1], Paul Lombroso[2], Yves De Koninck[6], Eve Tsai[7], Michael Hildebrand[8]

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The prevalence of many chronic pain syndromes differs across sex. Recent studies have identified differences in immune signalling within spinal nociceptive circuits as a potential mediator. Although it has been proposed that sex-specific pain mechanisms converge once they reach neurons within the superficial dorsal horn (SDH), direct investigations using rodent and human preclinical pain models have been lacking. Here, we discovered that in the Freund's Adjuvant in vivo model of inflammatory pain, where both male and female rats display tactile allodynia, a pathological coupling between loss of inhibition and NMDA receptor potentiation within SDH neurons was observed in male but not female rats. Unlike males, the neuroimmune mediator BDNF failed to downregulate inhibitory signalling elements and upregulate excitatory elements in female rats, resulting in no effect of ex vivo BDNF on synaptic NMDA receptor responses in female lamina I neurons. Importantly, this sex difference in spinal pain processing was conserved from rodents to humans. As in rodents, ex vivo spinal treatment with BDNF downregulated markers of disinhibition and upregulated markers of facilitated excitation in SDH neurons from male but not female human organ donors. Ovariectomy in female rats recapitulated the male pathological pain phenotype. The discovery of sexual dimorphism in a central neuronal mechanism of chronic pain across species provides a foundational step towards a better understanding and treatment of pain for both sexes.

2-D-231: Cortical contributions to transsaccadic discrimination of object orientation vs. shape changes: An fMRI paradigm

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[1]York University

Here, we used a double-dissociation fMRI task to determine the cortical correlates for transsaccadic change detection of multiple object features. 21 participants fixated a cross ±15.4° of centre, where an object was subsequently presented (rectangle, barrel, or hourglass) oriented at ±45° from vertical. The fixation cross remained in the same position (Fixation condition) or shifted (Saccade condition), followed by the same object re-presented at the orthogonal orientation (Orientation change) or another object at the initial orientation (Shape change). Change in object orientation or shape in each trial was indicated via button press. After excluding 4 participants, a region-of-interest analysis on four regions (supramarginal gyrus, occipitoparietal junctional (OPJ), cuneus (Cu), and ventral temporo-occipital cortex) showed that only Cu presented significant eye movement and feature sensitivity, with only eye movement sensitivity in OPJ. A similar whole-brain univariate analysis was used to localize the optimal seed region for network analysis, which showed connections between left medial occipital cuneus and early-to-mid-level visual (e.g., lingual gyrus, superior occipital gyrus), object-relevant (e.g., medial occipitotemporal sulcus, transverse occipital sulcus), and oculo/sensorimotor (i.e., superior parieto-occipital cortex) regions. These results implicate medial occipital cortex in the transsaccadic memory and discrimination of multiple object features, with additional recruitment of regions in parietal and temporal cortex.

2-D-232: Electrophysiological properties of glutamatergic reticular and reticulospinal tract neurons of the medullary reticular formation important to locomotion

Yacine Haili[1], Josée Seigneur[1], Karimi Narges[1], Frédéric Bretzner[2]

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Recently, it has been shown that glutamatergic neurons of the medullary reticular formation integrate cortical and mesencephalic inputs and have access to the spinal locomotor circuit through the descending reticulospinal pathway. Although these neurons contribute to motor, locomotor, and postural functions, less is known about their electrophysiological properties and their network connectivity. Brainstems were harvested from 3-4-week-old VGluT2-cre mice for living tissue slice preparation. In a 1st series of experiments, we performed whole-cell patch-clamp recordings of reticular neurons. In a 2nd series of experiments, AAV2-retro-DiO-FP (fluorescent protein) was injected in the lumbar spinal cord to identify and patch glutamatergic reticulospinal tract neurons. In our 1st experiment, 42 neurons were recorded in the medulla, 30 of those neurons were located in the gigantocellular reticular nucleus (Gi). Most displayed a regular-spiking pattern (RS) with spike frequency adaptation and were identified afterwards as glutamatergic neurons. To investigate the network connectivity, we also recorded glutamatergic reticulospinal neurons projecting to the lumbar spinal cord. All these neurons showed a RS pattern with spike frequency adaptation. Most of these neurons also displayed a sag and low-threshold spikes in response to a hyperpolarizing current. Our results reveal the presence of reticulospinal tract neurons exhibiting regular firing pattern and spike frequency adaptation that could contribute to the descending motor command.

2-D-233: Gain adaptation and variability of vestibular corticothalamic neurons shape our perception of natural self motion stimuli

Jerome Carriot[1], Isabelle Mackrous[1], Graham McAllister[1], Hamed Hooshangnejad[2], Kathleen Cullen[2], Maurice Chacron[1]

[1]McGill University, [2]Johns Hopkins University

Natural stimuli display complex spatiotemporal characteristics. In order to encode such stimuli efficiently, sensory systems must continuously adapt by changing their response properties. The computational role of such adaptation remains poorly understood because adaptation can increase coding ambiguity. We investigated how vestibular thalamocortical neurons (VTN) and their afferent input within the vestibular nuclei (VON) respond to simple artificial and complex natural selfmotion stimuli in rhesus macaques. We found that both groups displayed comparable response properties to artificial stimuli which led to ambiguity. While such ambiguity persisted for artificial stimuli for VON, VTN instead faithfully followed the timecourse of natural selfmotion stimuli. A model including gain adaptation successfully reproduced our experimental data. Our results challenge the common wisdom that adaptation leads to ambiguity by showing that such adaptation actually leads to unambiguous encoding of natural stimuli. Second, we investigated the role of these VTN in the perception of selfmotion. We tested whether their responses can account for violation of Weber's law, i.e. discrimination performance is enhanced at higher stimulus amplitudes. While neural gain decreased as a function of stimulus amplitude, neural variability saturated at high values. As a result, neural populations thresholds saturated and agreed with perception. Taken together, we provide novel insights as to how variability and gain control contribute to encoding of natural stimuli with continually varying statistics.

2-D-234: Optogenetic expression in the cortical and subcortical areas of the non-human primate vestibular system

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Tabitha Bethany Jimenez[1], Manon St-Louis[1], Alfredo Ribeiro-da-Silva[1], Maurice Chacron[1]

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The transient sensations experienced by the vestibular system are critical for everyday activities such as gaze stabilization and the perception of self-motion. Accordingly, the investigation of vestibular neural coding would greatly benefit from the use of optogenetic methods; with which neuronal activity can be precisely and reliably modulated with high temporal precision. Due to our shared bipedality and close evolutionary origins, non-human primates (NHPs) are the ideal model animals. However, unlike application in invertebrates and rodents, optogenetic techniques using NHPs have not been well established, requiring researchers to infer the best approach. This project aims to provide robust results of NHP optogenetics in the vestibular system through in-vivo injection of an opsin adenovirus to key interconnected vestibular cortical and subcortical areas: the parietoinsular vestibular cortex (PIVC) and the vestibular nuclei in the brainstem of cynomolgus macaques. We can determine the efficacy and specificity of our vectors, chosen based on anatomical differences between the target regions, and evaluate opsin expression using histological methods such as immunohistochemistry and fluorescence microscopy. With the confirmation of histological expression, this project will open the door to confidently employing optogenetic methods to study vestibular electrophysiology and the behaviours it codes for, as well as to investigate feedback between our cortical and subcortical areas of interest.

2-D-235: Population coding of naturalistic self-motion in vestibular nucleus

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The vestibular system provides information about head motion in space and contributes to self-motion perception as well as stabilization of gaze and posture. The physiology of the vestibular system has been characterized mainly by studying single-unit recordings. Thus, our understanding of neural coding of vestibular perception and reflexes is limited because behaviors, in general, arise from the collective activities of neural populations rather than single cells. While two recent studies have examined population coding in the vestibular nucleus (VN), the stimuli used were either artificial or had low amplitude and frequencies. Natural stimuli, on the other hand, can reach high amplitudes and contain a range of frequencies, which can have a significant impact on population coding as observed in other systems. Studies in other sensory systems have shown that noise correlation and its relationship to signal correlation (i.e. correlation structure) can affect population coding significantly and in many different ways depending on factors such as stimulus (i.e. features, natural versus artificial stimuli), animal's attentional and arousal state, etc. Accordingly, we will investigate the population coding of natural self-motion in VN; We will simultaneously record from multiple vestibular only (VO) neurons during artificial and natural horizontal head motion in behaving rhesus monkeys and investigate population coding. Our results will likely be applicable for the development of neural prosthetics for patients with vestibular deficits.

2-D-236: Second-order attribute of head motion is encoded at single-neuron level in the vestibular nuclei

Isabelle Mackrous[1], Jerome Carriot[1], Maurice Chacron[1]

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[1]McGill University

Previous studies have focused on the encoding of the first-order features of vestibular stimuli, but few studies, to date, have studied the encoding of the second-order attribute that consist of changes in vestibular stimuli amplitude or envelope. Because envelopes are critical for perception, we investigated if and how vestibular only neurons in the vestibular nuclei, known to mediate self-motion perception, encode the envelope attribute of the head motion stimulus. Specifically, we studied neural responses to stimuli consisting of a noisy waveform whose envelope varied sinusoidally at lower frequency. Importantly, stimulus amplitude was kept low such as not to elicit static nonlinearities from afferents (e.g., rectification, saturation). Our results show that the envelope attribute of the stimulus is encoded at single-neuron level in the vestibular nuclei. On average, we found that the gain of the neuron's response to the envelope remained constant across frequencies ($p = 0.24$). Moreover, the neuron's response shows a slight phase lead that increases as the frequency of the envelope increases ($p=0.01$). We found that static nonlinearities do not account for neural envelope response. Finally, we calculated the discrimination threshold and found higher values than that found in the Thalamus and for perception. Overall, our results will have important implication in our understanding of how early processing of vestibular signal can encode second-order attributes of head motion that will further be used to ensure stable perception of the world and accurate motor control.

2-D-237: Neuronal sensitivity and variability mediate 3 parallel strategies for encoding natural translations in the primate vestibular system.

Mitchell Prostebby[1], Jerome Carriot[1], Isabelle Mackrous[1], Maurice Chacron[1]

[1]McGill University

Self motion is composed of both rotational and translational motions which occur with characteristic statistics in everyday life. In the context of rotation, we have previously shown that neurons at the first central stage of vestibular processing (VN) are adapted to match their tuning curves to the statistics of natural rotation. This strategy effectively removes redundancy in the neural response, and produces responses which are independent of frequency (i.e. temporally whitened). However, unlike for rotation, translation sensitive neurons display significantly more heterogeneity in their tuning curves to artificial stimuli, and their responses to natural stimuli which cover the full physiological range of motion frequencies has not been explored. Here we investigated whether and, if so, how the responses of translation sensitive vestibular-only (otolith VO) cells in the VN of awake behaving macaques are adapted to naturalistic translation stimuli. Our results indicate that otolith VOs are not consistently matched to natural statistics in the same way as their rotation-sensitive counterparts, and instead fall roughly into 3 categories covering a range from strongly low-pass filtered to optimally whitened responses. This study is the first to examine the responses of otolith VO neurons in the context of natural self-motion, and suggests that low-pass filtered, faithful reconstruction, and optimally encoded representations of the stimulus may each be implemented in the translational vestibular system via parallel encoding strategies.

E - Homeostatic and Neuroendocrine Systems

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2-E-238: Sex-specific modulation of acute cerebrovascular responses to photothrombotic stroke in mice requires rho-kinase

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Rho-kinase (ROCK) is a major regulator of endothelial function. Pharmacological blockade of ROCKs and heterozygous deletion of ROCK2 (isoform predominant in the brain endothelium) are neuroprotective in ischemic stroke. Regulation of cerebral blood flow (CBF) following ischemic stroke is not well characterized in animal models. The aim of this study is to determine the contribution of ROCK2 to regulation of CBF following stroke between Wild-Type (WT) and ROCK2+/- male and female mice. In sham or gonadectomized male and female mice, CBF was measured using laser Doppler flowmetry before and after photothrombotic (PT) stroke. Intact WT females showed an immediate 50% reduction in CBF following PT, whereas intact WT males surprisingly showed no immediate drop. At 48 hours post-PT, CBF values in intact WT males and females became comparable, both reduced by ~50% from pre-stroke values. Gonadectomy of WT female mice resulted in similar CBF patterns as intact WT males. Male and female ROCK2+/- mice displayed similar CBF responses as intact WT females. Gonadectomy of males did not change the acute CBF responses to PT stroke. Infarct volumes measured by MRI at 48 hours post-PT did not differ between groups. CBF is primarily regulated by vasomodulators secreted from endothelial cells. Interestingly, ROCK2+/- mice are characterized by constitutively-increased endothelial nitric oxide synthase (eNOS) expression, an important vasomodulator. As eNOS is largely regulated by estrogens, it may therefore be partly responsible for our results, which will be the focus of subsequent studies.

2-E-239: Prostaglandin E2 alters intracellular chloride homeostasis to drive neuroendocrine stress response to immune challenges

Sam Mestern[1], Wataru Inoue[1]

[1]University Of Western Ontario

Immune-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis is driven by an inflammatory mediator prostaglandin E2 (PGE2) mediated by two of its receptor subtypes EP1 & EP3. We recently showed that PGE2-EP3 signaling excites HPA axis regulatory neurons [corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN)]. EP1-mediated mechanisms remained unsolved. The excitability of PVN-CRH neurons are constrained by GABAA mediated synaptic inhibition that relies on low-level intracellular Cl-. We hypothesized that PGE2-EP1 signaling increases intracellular Cl-, causing a depolarizing shift in the reversal potential of GABAA (EGABA) mediated synaptic currents. Using gramicidin perforated patch-clamp recordings and focal application of GABAA receptor agonist muscimol, we examined the reversal potential of GABAA receptor-mediated currents from CRH neurons in acute mouse slices. The change in EGABA was measured before, and at several points after the bath application of PGE2, an EP1 Agonist, and vehicle. PGE2 induced a significant depolarizing shift in the reversal potential of GABAA receptor-mediated current. The depolarizing shift was slow to develop and peaked around 40 min post PGE2. EP1 agonist caused a similar, slowly developing depolarizing shift. The vehicle showed no change in EGABA. Our results support our hypothesis that PGE2-

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EP1 coupling induces a slow depolarizing shift in EGABA, which complements the rapid effects of PGE2-EP3 signaling, for the excitation of PVN-CRH neurons during inflammation.

2-E-240: Recurrent inhibition modulates the activity of stress responsive neurons in the paraventricular nucleus of the hypothalamus

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Corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) are a key node of stress information processing that drives the neuroendocrine response via activity-dependent release of CRH into the blood. However, little is known about the single-cell firing properties of PVN-CRH neurons in vivo that regulates this hormone output. We used a combination of optogenetics and electrophysiology to "tag" the in vivo firing activity of CRH neurons. In anesthetized mice, we first recorded the spontaneous single-unit firing activities of PVN neurons during a no-stress baseline and following sciatic nerve stimulation (stress). In the same mice, light-induced single unit activity from ChR2-expressing CRH neurons was recorded. The latter recording provided fingerprint waveforms of light-responding PVN-CRH neurons, allowing us to identify PVN-CRH neurons from spontaneous recordings. Light-responsive PVN-CRH single unit activities were recorded (n = 18). These "identified" units revealed that PVN-CRH neurons can fire in two modes - brief, rhythmic bursts (>100 Hz) and single-spike firing. These rhythmic bursts have long (~1s) inter-burst intervals that constrain the average firing rate of the cell while single spiking is permissive for higher firing activities. Our computational network model shows that the firing patterns can be generated by recurrent CRH-GABA interactions. Both in vivo and in silico data show that the switch from rhythmic bursting to single spiking underlie stress-induced high-activity state which may be relevant for hormone release.

2-E-241: Mechanisms of MDMA induced vasopressin release in rats

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Clinical data proposes that the common street drug MDMA (ecstasy) increases water intake by inducing the sensation of thirst and promoting fluid retention by the kidney. These effects account for the high incidence of hyponatremia (low blood sodium and excel water in serum) in patients visiting hospital emergency departments as a result of experiencing headaches and dizziness (and other signs of hyponatremia) following ingestion of MDMA. Clinical as well as rodent studies also reveal an increase in serum vasopressin levels when MDMA is ingested or administered, which is likely a key factor in fluid retention. To investigate the neurophysiological mechanisms underlying these effects brain slices obtained from transgenic rat brains were prepared at a specific angle to preserve circuitry important for the regulation of thirst and vasopressin release. Whole cell current and voltage clamp recordings from identified vasopressin neurons revealed that a bath application of MDMA causes an excitatory response; mediated by membrane depolarization. Moreover, a proportion of tonically active vasopressin neurons were observed to transition to a phasic firing pattern

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known to facilitate peptide release. These results suggest that MDMA can act directly on neurons controlling vasopressin thereby increasing the likelihood of fluid retention.

2-E-242: Fasting induces remodeling of hypothalamic neuronal circuits controlling food intake in a growth hormone secretagogue receptor-dependent manner

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Introduction. Arcuate nucleus (ARC) neurons producing Agouti-related peptide and neuropeptide Y (AgRP/NPY) innervate the hypothalamic paraventricular nucleus (PVH) to control food intake and energy balance. Some neuronal circuits undergo morphological remodeling under specific conditions. Under fasting, the ghrelin receptor (or growth hormone secretagogue receptor, GHSR) is up-regulated and activates the AgRP/NPY neurons. Here, we hypothesized that the AgRP/NPY projections to the PVH would undergo morphological remodeling during fasting in a GHSR-dependent manner. Methods. We performed fluorescent immunostainings and DiI axonal labeling in brains of fed or fasted mice with pharmacological or genetic blockage of the GHSR signaling and then estimated the AgRP/NPY fibers density in the PVH. Results. We found that 1) AgRP/NPY fibers density increase in the PVH of fasted mice, 2) the morphological remodeling of the AgRP/NPY fibers to PVH correlates with the PVH neuronal activation, and 3) PVH neurons are not activated in ARC-ablated mice. We also found that fasting-induced remodeling of AgRP/NPY fibers to PVH and PVH activation are impaired in mice with pharmacological or genetic blockage of GHSR signaling. Discussion. We provide evidence indicating that the AgRP/NPY fibers to PVH undergo morphological remodeling under fasting and that GHSR signaling is required for these effects. Thus, we show that connectivity between hypothalamic circuits controlling food intake is highly plastic in the adult brain and reveals a novel role for the GHSR signaling.

2-E-243: Topographical and temporal patterns of activation in the basolateral amygdala in response to stress

Robert Aukema[1], Gavin Petrie[1], Samantha Baglot[1], Benjamin Lau[1], Lauren Seabrook[1], Maria Morena[1], Sandra Kadhim[1], Andrei Nastase[1], Stephanie Borgland[1], Matthew Hill[1]

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The basolateral amygdala (BLA) is a critical brain structure involved in emotional processing. Both rewarding and aversive stimuli activate the BLA, and the BLA can drive both appetitive and aversive responses. Notably, the BLA exhibits strong heterogeneity in expression of projection populations, such that different regions of the amygdala project to different downstream targets. This collectively suggests that aversive stimuli may recruit a specific spatial and temporal pattern of activation in the BLA in order to guide an appropriate behavioral or physiological response to stress. First, we characterize the endocrine response of adult male rats to six different stimuli: swim stress, restraint stress, mild aversive foot shock, bobcat urine, citral odor, and goldfish crackers. We then identify distinct spatial and temporal patterns of activation within the BLA for each of these stimuli using c-fos expression mapping and fiber photometry. Next, we use restraint stress as a model to demonstrate that chemogenetic inhibition of the BLA during stress exposure reduces stress-

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induced release of corticosterone. Finally, we demonstrate that optogenetic stimulation of the BLA in the absence of external threat is sufficient to elicit a neuroendocrine response. Collectively, this suggests that stressful stimuli elicit a unique spatiotemporal pattern of activation in the BLA, and that activation of the BLA is both necessary and sufficient for generating an endocrine response to aversive stimuli. This is important to guide future work in dissecting the neural circuity underlying the stress response.

F - Cognition and Behavior

2-F-244: Role of nicotinic receptors in the perirhinal cortex in memory modulation by nicotine, cocaine, and their conditioned stimuli

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Our research group has recently reported that nicotine, cocaine, and their conditioned contextual stimuli (CS), enhance object memory consolidation via noradrenergic and dopaminergic receptors. This suggests the hypothesis that the neuropharmacology of unconditioned and conditioned memory modulation is not influenced by drug class. To test the hypothesis, male Sprague-Dailey rats received infusions of the nicotinic receptor antagonist mecamylamine (MEC) within the perirhinal cortex (PRh); a cortical region well known to be involved in consolidation object memory. To establish the drug CSs, rats were confined for 2 h in a chamber (the CS+) after injections of 0.4 mg/kg nicotine or 20 mg/kg cocaine, and in another chamber (the CS−) after injections of vehicle. This was repeated over 10 d (5 drug/CS+ and 5 vehicle/CS− pairings in total). Surprisingly, it was found that the memory enhancing action of post-sample 0.4 mg/kg nicotine, but not 20 mg/kg cocaine, was blocked by intra-PRh infusions of 10 and 30 µg/side MEC. Moreover, the memory enhancing effects of the nicotine CS, but not cocaine CS, were also blocked by 30 µg/side MEC. Overall, these data indicate that a nicotine CS promotes memory consolidation by enhancing PRh cholinergic activity similar to the central effects of nicotine itself, but this is not the case for cocaine and cocaine CSs. These results suggest that in addition to mimicking the behavioural effects of drugs, drug CSs also possess the ability to mimic the neurochemical effects of the drugs themselves on object memory consolidation. Supported by NSERC.

2-F-245: A quantitative comparison of fMRI and fNIRS activity to a median nerve stimulation task

Karnig Kazazian[1], Androu Abadalmalak[1], Loretta Norton[1], Teneille Gofton[1], Derek Debicki[1], Adrian Owen[1]

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Functional Magnetic Resonance Imaging (fMRI) and functional Near Infrared Spectroscopy (fNIRS) are neuroimaging techniques that can measure changes in blood flow in response to external stimuli. fNIRS is a portable imaging device and considered to be the optical equivalent of fMRI. The objective of this preliminary work is to investigate the ability of fNIRS to detect brain activity during a median nerve stimulation task in healthy controls and to

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compare the results to fMRI findings. To date, 25 healthy controls have been recruited to the fMRI task, of which 10 have also participated in the fNIRS task. Median nerve stimulation was conducted while brain activity was recorded with fMRI and fNIRS (tests done sequentially). Both the left and right hand were stimulated, successively, at a current that sustained thumb abduction (8-35 mA). A block design with eight cycles of stimulation 'on' and seven cycles of 'rest' was used. At the group level, for both fMRI and fNIRS, significant brain activity was observed in the contralateral primary and bilateral secondary somatosensory areas for each hand being stimulated. At the single subject level, the results demonstrate an 80% agreement between fMRI and fNIRS results where fMRI is considered ground truth. The overall good agreement between the two techniques is promising, and future work will focus on recruiting additional participants to better assess the sensitivity between modalities. Ultimately, this work adds to the growing body of research highlighting fNIRS as a suitable alternative to fMRI, as it affords the advantage of being portable and low-cost to maintain.

2-F-246: Representation of 3D space in the hippocampus of freely moving marmosets

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The role of the hippocampus in representing space is widely supported. Neurons that increase their firing rate when an animal occupies a certain region, 'Place Cells,' have been thoroughly identified and studied in multiple species. This unique population of neurons has been thought to support a cognitive-map like representation of space in the brain; however, little is known about how these representations are formed in the common marmoset during free navigation in a 3D environment. Moreover, whether these representations are modulated by spatial view or movement kinematic has yet to be determined. In this work, we sought to identify the firing properties of neurons in the CA fields of the hippocampus while we register spatial and view information of freely navigating marmosets as they engage in a variety of foraging behaviors in 3D space. For this purpose, we habituated the experimental subjects to freely move inside a plexiglass recording chamber with four vertical levels while wearing affixed infrared reflective markers on top of skull implants that allowed for 6 degrees of freedom position and head direction camera tracking (Optitrack, Natural Point Inc, USA). Using MRI-guided neuro-navigation techniques, we chronically implanted 32ch microwire arrays in the hippocampus, and we were able to record single-unit activity during the aforementioned behaviors wirelessly. We analyzed data from 2 animals; spatial view and occupancy rate maps were constructed using 20cm3 bins. Spatial Information Content (SIC) was calculated independently for place and view for 200 total cells. SIC was higher for the spatial view than body position. We also found cells whose firing rate was highly correlated for both body velocity and head angular velocity.

2-F-247: Development of spontaneous tests of olfactory, object, and social discrimination behaviour in male golden hamsters: use in rodent models of SARS-CoV-2 infection?

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While the SARS-CoV-2 virus is well known for its impact on the respiratory system, neurological symptoms such as headache, anosmia, and cognitive impairments have been observed. Most strikingly, anosmia is reported in around 50% of COVID-19 cases. Male golden hamsters are used to study the outcomes of SARS-CoV-2 infection and therefore may also be used to model the neurological and behavioural effects of following virus challenge. To this end, we are developing a behavioural battery that could easily be run by any scientific group in containment level 3 to assess behavioral changes in hamsters following SARS-CoV-2 infection. All tasks rely on rodents' innate preference for novelty and are conducted without extensive training or rule learning. Briefly, hamsters are exposed to two copies of a stimulus (odour or object) in a training trial. Following a brief delay, the hamsters are re-exposed to a third copy of the now familiar stimulus, and a novel stimulus. Results indicate that hamsters show a preference for novel odours; however, they are unable to perform the object-based task. In a sociability task, male hamsters were found to preferentially explore a novel hamster more than a novel object, as well as discriminate between a novel and familiar hamster in a similar paradigm. Experiments to refine these tasks are ongoing, with a goal of incorporating them into SARS-CoV-2 vaccine trials at the Vaccine and Infectious Disease Organization/Intervac in the fall of 2021.

2-F-248: Investigating the influence of perineuronal nets surrounding parvalbumin-positive neurons in sensorimotor circuitry on motor performance

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Perineuronal nets (PNNs) are extracellular matrices that preferentially surround parvalbumin-positive (PV+) interneurons. Since PV+ neurons shape neural dynamics and plasticity, PNNs surrounding PV+ neurons have been proposed to regulate neural function. Much of the research on PNNs has centered on their role in sensory circuits, and little is known about how PNNs in sensorimotor structures affect behavioral expression. Here, we analyze the relationship between PNN and PV expression in sensorimotor systems and vocal performance in songbirds. Because songbirds, like humans, learn their vocalizations and use auditory feedback for vocal learning and control, songbirds are powerful animal models to reveal neural mechanisms of sensorimotor plasticity and function. We specifically relate PNN expression around PV+ neurons in forebrain and basal ganglia circuitry to the performance of learned vocalizations in the zebra finch. We hypothesize that, just as PNNs in sensory processing areas consolidate the sensory representations, PNNs in sensorimotor structures could consolidate sensorimotor commands for vocalizations. In this respect, we propose that more PV+ neurons are surrounded by PNNs in birds that produce more stereotyped vocalizations. Given that developmental exposure to song and age affect song stereotypy, we investigate this relationship in juvenile and adult birds that are either reared normally or deprived of song exposure throughout development. Our studies hope to provide further insight into the influence of PNNs on behavioral control and plasticity.

2-F-249: Use of spontaneous object- and odour-based working memory (WM) tasks to evaluate the effects of acute cannabis smoke exposure on WM capacity in male rats

Ilne Barnard[1], Dan McElroy[1], Spencer Orvold[1], Timothy Onofrychuk[1], Faith Austin-Scott[1], Emma Morelli[1], Robert Laprairie[1], John Howland[1]

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With the recent legalization of cannabis in Canada, there is concern that its use may perpetuate negative outcomes in mental health and impact executive brain functions like working memory (WM). The endocannabinoid (eCB) system regulates the homeostasis of the circuitry underlying memory processes. We were interested in investigating the effects of acute cannabis smoke (Mohawk strain, high-THC; Treasure Island strain, low-THC) exposure on adult male Long-Evans rats' WM capacity. We used a validated object paradigm to evaluate visuospatial WM capacity. Then, we developed a novel odour-based paradigm for assessing olfactory WM capacity as it is rodents' primary sense. An identical (IOT) and differential (DOT) version of the paradigms allowed us to evaluate various cognitive loads on WM capacity using 3 and 6 items. The spontaneous WM tasks used capitalize on rodents' innate preference for novelty and the time spent exploring familiar stimuli in the sample phase, and novel stimuli introduced in the test phase, was analyzed. In both the object and odour paradigms, a load-dependent effect on memory was found whereby more stimuli notably decreased WM function in the DOT, but not IOT, versions. Following acute smoke exposure, no overall disruption in WM function was observed in the object paradigm. However, WM deficits were observed in the odour paradigm after acute exposure to Mohawk, but not Treasure Island, smoke in both the IOT and DOT task. Due to this olfaction-based WM disruption, the task shows promise to model the cognitive impacts of cannabis consumption in humans.

2-F-250: Atrx deletion in microglia leads to memory deficits in mice

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Mutations in ATRX, a SWI/SNF-type chromatin remodeler, cause an intellectual disability syndrome associated with autistic behaviors in affected boys. We previously demonstrated that Atrx deletion in forebrain glutamatergic neurons leads to long-term spatial memory impairment (Cell Reports, 2020), whereas Atrx deletion in astrocytes causes long-term spatial and recognition memory deficits (unpublished). These studies suggest that ATRX has distinct functions in different brain cell types with varying outcomes on learning and memory. However, the contribution of another major glial cell type, microglia, has not yet been examined. To address this question, we generated male mice lacking ATRX exclusively in microglia using a tamoxifen-inducible Cre/loxP system. Tamoxifen (2mg/day) was injected daily for 5 days in 45 day-old control and ATRX knockout mice (Atrx miKO). Immunofluorescence staining of brain sagittal cryosections revealed >90% ATRX knockout efficiency in microglia across different brain regions. A battery of behavior tests was performed on Atrx miKO and control mice. Atrx miKO exhibit normal locomotor activity, working memory and associative memory in the open field, Y maze and fear conditioning tests, respectively. However, Atrx mi-KO mice showed an anxiolytic effect in the light/dark box and Elevated Plus Maze tests. In Morris Water Maze test, the Atrx miKO showed long-term spatial memory deficit. In Novel Object Recognition test, Atrx miKO showed both short-term and long-term recognition memories deficits. These findings demonstrate that ATRX-null microglia negatively impact spatial and recognition memory and has anxiolytic effects in adult male mice and highlight a microglia-specific role of ATRX in intellectual disability.

2-F-251: Sex-specific effects of adolescent omega-3 supplementation and environmental enrichment on adulthood coping mechanisms and glucocorticoid receptor expression in Wistar rats

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The adolescent brain displays enhanced neuroplasticity which can impact ulterior coping mechanisms and physiological responses to stressful situations. In fact, both omega-3 supplementation and exposure to enriched environments (EE) have shown promising ability to regulate and normalize the stress response. To our knowledge, no studies have examined the synergistic effects of treatments when administered during this critical period. To do so, male and female Wistar rats (each n=32) arrived at facility at postnatal day (PND) 23 and were left to acclimate until onset of daily oral gavage of omega-3 via menhaden fish oil (FO; 0.3 mL/100 g body weight) or control soybean oil (CSO) from PND 28-47 and of exposure to EE or regular cages (RC) from PND 28-59. Weekly blood samples were taken during gavage for corticosterone analysis. As adults, rats were exposed to the Forced Swim Test (FST - PND 90-91). Brain tissue was collected on PND 95 for quantification of glucocorticoid receptor (GR) expression in the hippocampus CA1 and CA3 regions by immunofluorescence. Interestingly, FO diet increased FST coping behaviours in females while EE favoured energy conservation in males. Female rats showed higher corticosterone levels during the last week of supplementation when compared with males. Females and FO-treated rats showed reduced CA3 GR expression and, when compared to controls, FO and EE individually decreased GR expression in that region. This study highlights specific ways in which adolescent omega-3 and EE exposure promote energy conservation and coping mechanisms in adulthood.

2-F-252: A positive allosteric modulator of M1 Acetylcholine receptors improves pathology and cognitive deficits in female APPswe/PSEN1ΔE9 mice

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Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by progressive cognitive decline with no effective treatments to slow progression. Beta-amyloid (Aβ) protein is considered the principal neurotoxic species in AD brains. The m1 Acetylcholine receptor (m1 mAChR) plays a key role in memory and learning. m1 mAChR agonists shows pro-cognitive activity but cause many off target adverse effects including seizures. A new m1 mAChR positive allosteric modulator (PAM), VU0486846, is devoid of direct agonist activity and adverse effects but was not tested for efficacy in AD mice. Since women account for more than 60% of cases and most AD research is conducted in male models, we tested the efficacy of VU0486846 in female AD mice first. Here, we treated 9-month-old female APPswe/PSEN1ΔE9 (APPswe) and wild-types with VU0486846 in drinking water (10mg/kg/day) for 4 or 8 weeks. Cognitive function of all mice was assessed after treatment and brains were harvested for biochemical and immunohistochemical assessment. Both 4 and 8 weeks of treatment with VU0486846 improved cognitive function of APPswe mice when tested in novel object recognition and Morris water maze. This was paralleled by a significant reduction in hippocampal Aβ oligomers and plaques. VU0486846 did not change the expression of amyloid precursor protein in APPswe but the reduction in Aβ load in VU0486846-treated mice was due to a shift in the processing of amyloid precursor protein from β-cleavage to non-amyloidogenic cleavage. Specifically, VU0486846 reduced expression of β-secretase 1 (BACE1) whereas enhanced expression of the α-secretase

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ADAM10 in APPswe hippocampus. Thus, using m1 AChR PAMs can be a viable disease-modifying approach that should be exploited clinically to slow AD.

2-F-253: Developmental patterns for memory-guided attention in children and adolescents

John DeJesus[1], Maya Rosen[2], Katie McLaughlin[2]

[1]York University, [2]Harvard University

Human attentional capacity is severely limited. Memory-guided attention (MGA) is an adaptive process that uses past experiences to effectively direct attention. Adults visually attend faster with MGA compared to an external visual cue (e.g. arrow). We focus on understanding the gap in how MGA changes across development. We hypothesized that 1) young children have faster reaction times (RT) for stimulus-cued attention (SCA) compared to MGA, and 2) as age increased, RT for MGA would be faster compared to SCA. A sample of children and adolescents (n=75) ages 5 to 16 (M: 10.82 ± SD: 3.40) was recruited in Seattle, Washington. Participants completed two attention tasks: SCA and MGA. The SCA task presented a target <I>word</I> (e.g. "apple") and an arrow directing their attention to one of four quadrants, a brief delay, then an image appeared at each quadrant for participants to respond whether the target <I>image</I> appeared in the correct location. The MGA task was identical except they learned pairings of objects with specific quadrants and used memory to direct their attention instead of an external cue. Mean RT and accuracy on validly and invalidly cued trials were collected. Linear regression indicated age significantly predicted RT differences scores (RTMGA - RTSCA) in validly cued trials, <I>B</I> = -16.107, <I>t</I>(73) = 2.849, <I>p</I> = .006. Age was not a significant predictor for invalidly cued trials. Our findings contribute to understanding the developmental patterns of MGA. Specifically, children attend to SCA faster than MGA, though faster to MGA compared to SCA as they age towards adulthood.

2-F-254: Hippocampal CA1 network supports more cell assemblies in young and non-remapping rats

Jennifer Eseonu[1], Karim Ali[1], Seth Campbell[1], Lesley Schimanski[2], Carol Barnes[3], Stephen Cowen[3], Masami Tatsuno[1]

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It has been hypothesized that cell assemblies represent mental or perceptual entities, forming the basis of neural coding and computation. We investigated how the number of cell assemblies was related to the age of the rats and spontaneous remapping, using unit recordings of CA1 pyramidal cells in six young and six old rats while they learned a place-dependent eyeblink conditioning task (Schimanski et al., 2013). To control the dependence of cell assembly detection on different number of recorded neurons, we selected 30 pyramidal cells randomly from each recording session and repeated the procedure 25 times. This generated >8000 data sets. The number of cell assemblies was estimated by a recently proposed method (Russo and Durstewitz, 2017). We found that young rats had significantly more cell assemblies than old ones (median for young = 166.7, median for old = 87.4, Mann-Whitney test, p = 3.1 x 10-8). Significantly more cell assemblies were also detected in non-remapping rats than remapping ones (median for non-remapping = 192.1, median for remapping = 90.9, Mann-Whitney test, p = 8.4 x 10-13). Interestingly, cell assemblies were

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most abundant in the first few days of recording if rats were grouped into non-remapping, young or old, but not in remapping. Taken together, we showed that significantly more cell assemblies were detected in young and non-remapping rats. Reduction of cell assemblies over training in non-remapping rats suggests that efficient neural codes may be generated by learning and hence a reduced number of cell assemblies is sufficient.

2-F-255: Effects of smoked cannabis and injected Δ9-tetrahydrocannabinol on touchscreen-based tasks for measuring working memory, attention, and impulsivity in male Long Evans rats.

Dan McElroy[1], Ilne Barnard[1], Timothy Onofrychuk[1], Thaísa Sandini[1], Andrew Roebuck[1], Faith Austin-Scott[1], Ashton Heidt[1], Robert Laprairie[1], John Howland[1]

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Behavioural neuroscience researchers continue to seek relevant rodent paradigms that mimic human patterns of cannabis use. Injected Δ9-tetrahydrocannabinol (THC) is commonly used to assess acute cannabis effects in rodents despite pharmacokinetics varying greatly between injection and inhalation. In addition, tasks used to assess behaviour following cannabis exposure often lack strong translational relevance to human tasks. Therefore, in the present experiment, we investigated cognitive effects of acute exposure to cannabis smoke in two rodent tasks highly translatable to human tasks for measuring working memory, attention, and impulsivity. Male Long-Evans rats were trained in two cognitive tasks using touchscreen-equipped operant conditioning chambers: (1) the trial-unique, delayed nonmatching-to-location (TUNL; n=16); (2) the five-choice serial-reaction time task (5CH; n=16). Trained rats received: (i) combusted cannabis smoke (two strains: Mohawk, high-THC; Treasure Island: low-THC) using a 4-chamber pump-driven system; or (ii) injected THC (3.0mg/kg; i.p.) and behaviour was immediately assessed on the tasks. Interestingly, we failed to observe any effects of cannabis smoke on performance of TUNL or 5CH; however, injected THC significantly reduced accuracy and number of trials completed during TUNL, plus a notable (albeit insignificant) increase in omissions during 5CH. These data support a growing literature showing distinct differences between cannabis strain and method of administration, highlighting a continued need to investigate cannabinoid effects on cognition.

2-F-256: Identification of musical instrument sounds under noise masking

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The functioning of timbre and other form-bearing dimensions in music depends on the acoustic generation of sound, as well as physiological responses and the psychological organization of the information carried by sound. Human hearing can be reshaped by individual experience and can even be affected by cultural circumstances. To understand how hearing loss can affect the perception of timbre, we adopted noise maskers of varying kinds into a one-interval 2AFC task measuring the performance of timbre identification. Stimuli were presented using participant's personal laptop over headphones/earphones. In each trial, either a 300-ms trumpet or clarinet note at 440-Hz fundamental (target) with the same pitch was embedded in the middle of a 1-second Gaussian noise (masker). Three types of noise were used: broad-band noise, low-pass noise filtered at 4 kHz, and band-pass

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noise filtered between 5 kHz and 9 kHz. The target was fixed at one sound level, while the maskers of each kind were attenuated to 3 different levels. Our preliminary results show that (1) performance on the timbre identification task can be undermined by increasing the masker level and (2) noise maskers through a low-pass filter are as effective as broadband noise maskers but not those through a band-pass filter, suggesting that lower frequencies contribute more to identification. In future studies, we will further refine the composition of the noise masker, in both spectral and temporal domains, to explore how acoustic features contribute to timbre perception.

2-F-257: The effects of outdoor versus indoor exercise on psychological health, physical health, and exercise behaviour: a systematic review of longitudinal trials

Matthew Noseworthy[1], Luke Peddie[1], E. Jean Buckler[1], Faith Park[1], Margaret Pham[1], Spencer Pratt[1], Arpreet Singh[1], Teresa Liu-Ambrose[1], Eli Puterman[1]

[1]University of British Columbia

Background: Evidence suggests that the health benefits of exercise may be enhanced when performed outdoors in nature, as compared to indoors. Aim: To compare the effects of longitudinal exercise trials in outdoor versus indoor environments on psychological and physical health, and exercise behaviour. Methods: We searched 9 databases from inception to December 2019 for English-language, peer-reviewed articles. We included randomized and non-randomized trials that compared ≥2 bouts of outdoor versus indoor exercise and assessed ≥1 main outcome related to psychological or physical health, or exercise behaviour. We assessed risk of bias with the Revised Cochrane risk-of-bias tool for randomized trials. Due to outcome heterogeneity, we performed a narrative synthesis. Results: We identified 4 eligible trials from 6 papers. Exercise sessions, where reported, involved 45-60 minutes of running or mixed aerobic and resistance training, at moderate to high intensity. All trials assessed both psychological and physical outcomes, while two trials also assessed exercise behaviour. In total, 88 comparisons were made between outdoor and indoor environments, including 22 statistically significant comparisons, all favouring outdoor exercise. Interpretation of results was hindered by a high risk of bias in all papers, unclear reporting, and high outcome heterogeneity. Conclusion: There is limited evidence for health or behavioural benefits of long-term exercise in outdoor environments, as compared to indoors, indicating a need for future, high-quality longitudinal trials with larger samples.

2-F-258: Functional brain network for presaccadic visual processing: evidence from high resolution EEG and graph theory analysis

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The cortical mechanisms for presaccadic signal processing remain poorly understood at the network level, in particular how they interact with simultaneously presented visual stimuli. Here, we used graph theory analysis (GTA) to construct and evaluate functional brain networks based on EEG data collected in the perisaccadic interval. EEG was recorded via 64 channels in two behavioral conditions (fixation or saccade). Participants (N=21) were pre-cued with a series 1-3 grids (three horizontal lines, 10° by 10°) located 5° below the central fixation-point. 100ms later, a stimulus (three vertical lines; same size/location) was briefly presented (for 70ms). In the saccade condition, a left/right shift of the fixation-point during

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the interstimulus interval triggered a saccade after the second stimulus. Source localization (SL) was performed on the 200ms period following the saccade cue, or the equivalent time during fixation trials. Lagged coherences were calculated between all pairs of 84 Brodmann areas. SL/GTA identified major network hubs near the frontal and parietal eye fields, with widespread cortical connectivity. Other GTA measures (clustering coefficient, global efficiency, energy, entropy) showed that network segregation, integration, synchronizability, and complexity were enhanced during the perisaccadic interval. Further, these network properties significantly interacted with stimulus repetition, altering both hubs and network topography. These data suggest a network mechanism for enhanced visual information processing and propagation in the presaccadic interval. Acknowledgements: Grant Support: an NSERC Discovery Grant and VISTA Fellowship, funded by CFREF.

2-F-259: Distinct neuronal ensembles within the central nucleus of the amygdala regulate extinction learning

Belinda Lay[1], Mihaela Iordanova[1]

[1]Concordia University, CSBN

Correlational data from histochemical and physiological studies suggest that the central nucleus of the amygdala (CN) is involved in learning when expected events are omitted. Attempts at delineating the causal contribution of CN neurons to this learning have targeted the entire nucleus indiscriminately, disrupting the function of neurons. Recent research using selective approaches have uncovered that not all neurons within a brain area are recruited during learning. Rather, a specific neuronal ensemble supports learning with distinct subsets of neurons likely having different functional roles. We sought to determine the casual role of activated c-fos-expressing CN neurons in updating reward expectations during the omission of an expected reward using the Daun02 inactivation procedure. Male c-fos-lacZ transgenic rats were trained to expect the delivery of a food reward upon the presentation of an auditory cue. Subsequently, rats received non-reinforced exposure to the reward-associated cue to generate conditions of reward omission, that is extinction, and examine the effect of this on learning. Cell inactivation with Daun02 took place ninety minutes following the start of the non-reinforced session, presumably when the neurons that detected the reward omission were activated and the corresponding c-fos levels were at peak. This led to disruption in behaviour indicative of impaired retrieval of the extinction memory compared to rats that received a vehicle infusion, which left those neurons intact. Additional data show that further extinction learning was retarded in the absence of the neuronal ensemble in the CN, and resulted in greater spontaneous recovery and reinstatement. This disruption in behaviour was not due to drug diffusion into the basolateral amygdala.

2-F-260: Characterization of glutamatergic projections from raphe to hippocampus and their contribution to modulation of sharp wave ripples

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The hippocampus has an important role in learning and memory. Sharp wave ripples (SWR) in the hippocampus during slow wave sleep contribute directly to memory consolidation. The

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median raphe is known to modulate hippocampal rhythms and contains a glutamatergic long-range projecting population, characterized by the expression of type 3 vesicular glutamate transporter (VGLUT3), whose functions remain largely unexplored. In this study, we aim to provide the first exhaustive characterization of this raphe-hippocampus glutamatergic pathway and its contribution to SWR activity. First, using a combination of CRE-dependent retrograde viral vectors and VGLUT3-CRE mice we provide a detailed cartography of hippocampus-projecting glutamatergic neurons within raphe nuclei. We identify distinct glutamatergic pathways targeting the dorsal and ventral part of hippocampus. Second, we explored the contribution of glutamatergic neurons to SWR modulation. Electrophysiological recordings in the dorsal hippocampus of freely behaving mice during optogenetic activation of glutamatergic median raphe neurons shows strong inhibition of SWR activity. Control experiments showed no effect on SWR of light delivery in the median raphe. Our results suggest that glutamatergic inputs from the median raphe modulate hippocampus sub-regions and associated functions independently. In addition, we reveal a powerful inhibitory control of SWR through median raphe glutamatergic neurons, suggesting a strong impact of this pathway on memory formation and consolidation.

2-F-261: Hearing loss and cognition: using mouse models and automated touchscreen paradigms to uncover the mechanisms of noise-induced cognitive impairment

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Hearing loss is one of the most prevalent chronic health conditions affecting Canadians, with excessive exposure to loud noise contributing to this burden. Recent epidemiological studies have identified that hearing loss is a major risk factor for cognitive decline, and preclinical studies have suggested that the hippocampus is particularly sensitive to noise exposure. To further understand the deleterious effects of noise exposure on hippocampal function, we are investigating the relationship between pattern separation and noise-induced hearing loss in mice using a touchscreen task with high translational potential. Pattern separation is being assessed by training adult mice on a location discrimination task, in which two locations on the touchscreen are illuminated each trial, and across the testing session, the mice learn to nose-poke the correct location. Importantly, the difficulty of the task is increased by decreasing the distance between the two locations. Consistent with past studies on normal-hearing mice, at baseline our mice achieved the performance criterion in ~22 and ~30 trials during the 'easy' and 'hard' versions of the task, respectively. Baseline hearing sensitivity has been assessed using the auditory brainstem response, and the noise exposure protocol has been found to cause a moderate level of high-frequency hearing loss. Our ongoing work continues to test our prediction that noise exposure will only worsen performance of the 'hard' version of the task, and that the magnitude of hearing loss will correlate with the degree of impaired task performance.

2-F-262: Multiple object tracking scores predict post-concussion status years after mild traumatic brain injury

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The diagnosis of concussion remains challenging, particularly in cases where several months have passed between a head injury and clinical assessment. Tracking multiple moving objects in three-dimensional (3D) space engages many of the same cognitive processes that are affected by concussion, a form of mild traumatic brain injury (mTBI), suggesting that tests of 3D multiple object tracking (3D-MOT) may be sensitive to post-concussion syndrome after a brain injury has occurred. To test this, we evaluated 3D-MOT performance (using NeuroTrackerTM) against Sports Concussion Assessment Tool results for cognition, balance, and symptom severity in a large sample (N = 457) of male and female participants between the ages of 6 to 73. 3D-MOT performance in subjects under age 13 was not impaired by a history of concussion, but was positively associated with cognition and balance. 3D-MOT performance in those 13 and older was negatively associated with concussion symptom severity, and positively associated with cognition and balance. 3D-MOT was selectively impaired in subjects with probable post-concussion syndrome (pPCS), defined using the 95th percentile of symptom severity for subjects with no history of concussion. A decision tree predicted concussion status with 95.2% overall test accuracy (91.1% sensitivity, 97.8% specificity) using concussion history, age, and 3D-MOT score. Individuals with a history of concussion in the past 37 days were predicted to have pPCS if they were age 35 or older, or if they were under age 35 but achieved scores below 1.2 on the 3D-MOT. These results demonstrate the potential of 3D-MOT for pPCS diagnosis, and highlight the increased vulnerability to concussion symptoms that comes with age.

2-F-263: Prefrontal parvalbumin neurons facilitate the acquisition and performance of attention in mice

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Parvalbumin (PV) expressing neurons are a subclass of inhibitory cells that strongly regulate the activity of local excitatory neurons. PV neurons are important for maintaining excitation balance in the cortex and are involved in generating synchronous high frequency neuron firing. In the prefrontal cortex (PFC), disrupting the activity of PV neurons is associated with various cognitive impairments. The goal of this study was to assess the role of prefrontal PV neurons during focused visual attention in mice. We used the touchscreen rodent continuous performance task, which allows us to study various aspects of attention, including sustained attention, impulsivity, and visual discrimination. In vivo calcium imaging revealed that PFC PV neurons display increased activity prior to responding to the correct stimulus that increases through training. In vivo optogenetics was used to inactivate PFC PV neurons, or stimulate these neurons at a high (30hz) or low (5hz) frequency during the response phase of the task. When PV neurons were either inactivated or stimulated at 5hz, the animals' ability to attend to a target image was significantly reduced. Alternatively, stimulating PV neurons at 30hz significantly improved the animal's ability to attend to and discriminate the correct image, demonstrating a frequency specific bi-directional effect of PV stimulation. We also observe that an animal's baseline performance (high or low) is predictive of whether optogenetic manipulation can impair or enhance task performance, respectively. This implies that the effectiveness of optogenetic stimulation on altering attention may depend on the baseline organization of PFC activity, and that animals with unoptimized PFC function can be improved by high frequency stimulation of PV neurons.

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2-F-264: Impact of type 1 diabetes on brain capillary stalling and cognitive function in mice

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Introduction Recent work from our lab has shown that the brain capillaries routinely get clogged by cells and debris even under healthy conditions. The present study was undertaken to determine how type 1 diabetes affects this phenomenon and whether obstructions contribute to cognitive decline. Methods C57BL/6 mice were injected with streptozotocin to induce type 1 diabetes. These mice were implanted with cranial windows and cortical volumes were repeatedly imaged from 3-9 weeks after induction of diabetes. To model susceptibilities to short or long lived obstructions, we injected (i.v.) 5μm diameter fluorescent microspheres in diabetic and control mice at 30 minutes and 3 days before euthanasia. To determine the impact of diabetes on cognitive and sensorimotor activity, mice were subjected to a battery of behavioural tests. Results 2-photon imaging indicated that diabetic mice have higher rates of capillary stalling in somatosensory cortex that became more pronounced with duration of diabetes. Consistent with this, our fluorescent microsphere obstruction assay yielded significantly higher levels of capillary obstructions in diabetic mice. Behaviourally, diabetic mice were significantly impaired in learning and memory tests. Conclusions These studies suggests that diabetes is associated with greater risk for capillary obstructions in the brain as well as learning/memory deficits. Our future aims will provide a mechanistic understanding of how diabetes elevates one's susceptibility to capillary obstructions and cognitive decline.

2-F-265: Explicit attention to allocentric visual landmarks improves memory-guided reaching

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The presence of an allocentric landmark can have both explicit (instruction-dependent) and implicit influences on reaching performance (Byrne and Crawford 2010; Chen et al., 2011; Klinghammer et al. 2015, 2017). However, it is not known how the instruction itself (to rely either on egocentric versus allocentric cues) influences memory-guided reaching. Here, 13 participants performed a task with two instruction conditions (egocentric vs. allocentric), but with similar sensory and motor conditions. In both conditions, participants maintained fixation while a LED target briefly appeared (alongside a visual landmark) in one visual field. After a mask/memory delay period, the landmark re-appeared in the same or opposite visual field. In the allocentric condition, participants were instructed remember the initial location of the target relative to the landmark, and to reach relative to the shifted landmark. In the egocentric condition, subjects were instructed to ignore the landmark and point toward the remembered location of the target (50% of trials were motor-matched anti-reaches). The allocentric instruction yielded significantly more accurate pointing than the egocentric instruction, despite identical visual and motor conditions and regardless of the final pointing side. These results show that memory-guided pointing improves when participants are explicitly instructed to point relative to the landmark. This suggests that explicit attention to a visual landmark recruits allocentric coding mechanisms that are more resistant to memory decay than egocentric mechanisms.

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2-F-266: Astrocytes buffer fear memory

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Impaired emotion regulation forms the basis of several psychiatric disorders. The amygdala is an important brain region involved in the regulation of fear-related behaviours, and while much is known about the underlying neuronal mechanisms, the involvement of glial cells in this circuitry remain poorly understood. Hence, we aimed to clarify the role of astrocytes in the amygdala and the influence of these cells on fear learning and memory. To accomplish this, we used a combination of behavioral and genetic manipulations of astrocyte function in the lateral amygdala and assessed the corresponding effects on learning-independent (innate) and learning-dependent (conditioned) fear in mice. While we found that the impairment of astrocyte metabolic function seemed to have no effect on innate fear, it produced a persistent increase in the learned fear response of mice that was unhindered by a change in context. Additionally, we found that this effect was conserved across sexes. Our results suggest that astrocytes influence fear in a plasticity-dependent manner such that learning-dependent fear is specifically influenced by impaired astrocyte activity. These data highlight astrocytes as potential therapeutic targets for disorders characterised by the dysregulation of emotive states such as fear.

2-F-267: Neural and behavioural analyses of retrospective and prospective fear triggers

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Memories about aversive events (e.g. trauma) that elicit fear responses (i.e. primary triggers of fear) can propagate across the memory network, linking fear to other stimuli (i.e. secondary triggers of fear). This process can occur retrospectively and prospectively and is captured by sensory preconditioning and second-order conditioning, respectively. In sensory preconditioning two sensory stimuli are paired before one of those stimuli is paired with foot-shock. In second-order conditioning, sensory pairings occur after fear conditioning of one of the stimuli. In a series of studies, we show that pharmacological inactivation of the orbitofrontal cortex (OFC) prior to test for fear to the higher-order cues disrupts fear to the sensory preconditioned cue but enhances fear to the second-order cue. An investigation into the role of OFC input to the BLA and BLA input to the OFC during higher-order learning revealed that silencing OFC input to the BLA disrupted sensory preconditioning but not second-order conditioning. Silencing BLA input to the OFC, however, disrupted both effects. These results uncover a novel role for the OFC in higher-order fear and elucidate the interaction between the OFC and BLA in this learning.

2-F-268: Neurocognitive processes used in phonological and semantic priming: An ERP and oscillatory power study

Rachel Cochrane[1], Jonah Kember[1], Elizabeth Pang[2], Erin Panda[1]

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As we read, communication across brain networks allows us to integrate the way words look, sound, and mean. Phonological (sounds) and semantic (meaning) processing are key components of skilled reading. Understanding their underlying neural systems in adults sets a foundation to explore their development in children. In this pilot study, 64-channel EEG was recorded while adults (n=14; ages=23-36; 8 male) read word pairs that were rhyming or nonrhyming (goose-juice vs. small-juice) and semantically related or unrelated (open-close vs. nest-close). The goal was to explore both the event related potentials (ERPs) associated with lexical access (the N400) and oscillatory power effects associated with brain network integration during both types of priming. While similar N400 effects were seen for both phonological and semantic priming (larger N400 for unrelated vs. related words at central/mid-line electrodes 300-550ms; ps<.001), the frequency and duration of oscillatory power effects differed. Phonologically unrelated vs. related words showed greater power in beta (13-30 Hz, 334-820ms, p<.05), and gamma (31-80Hz, 292-456ms, p<.001), while semantically unrelated vs. related words showed greater long-lasting power in theta (4-7 Hz, 42-2400ms, p<.05), alpha (8-12 Hz, 122-1040ms, p<.05) and beta (13-30 Hz, 878-1544ms and 1944-2500ms, ps<.05). In line with speech processing models, higher frequency oscillations may be associated with sound as compared to meaning processing. Oscillatory power may reveal additional insights into the brain networks important for reading than ERPs alone.

2-F-269: Sex-specific blood-brain barrier alterations and vascular biomarkers underlie chronic stress responses in mice and human depression

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Major depressive disorder (MDD) will affect 20% of individuals and is now considered the leading cause of disabilities worldwide. However, most studies still investigate MDD exclusively in males. We reported that chronic social stress induces blood-brain barrier (BBB) leakiness through loss of tight junction protein claudin-5 (cldn5) in the nucleus accumbens (NAc), a mood regulation center, of male mice allowing the passage of circulating inflammatory mediators into the brain and establishment of depression-like behaviors. In rodents, exposure to chronic social defeat stress (CSDS) through physical encounter with a larger aggressive mouse induces a depression-like phenotype. A subpopulation of mice does not develop depressive behaviors and is considered resilient, allowing us to also study biological adaptations promoting stress resilience. After CSDS, cldn5 gene expression is unchanged in the NAc of stress-susceptible females but decreased in the prefrontal cortex (PFC), a brain region regulating decision making and social behaviors, when compared to controls and resilient mice. This sexual dimorphism of stress-induced neurovascular adaptations was confirmed in post-mortem human brain samples from depressed individuals, adding translational value to our findings. Viral-mediated functional manipulation confirmed the causality of cldn5 loss in the female PFC in the establishment of depressive behaviors and possibly sex-specific MDD symptomatology. This data suggests that stress-induced neurovascular changes do not occur in the same brain regions in stressed females vs males.

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2-F-271: Investigating the link between hearing loss and age-related cognitive decline in a rodent model

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Hearing loss is a chronic health condition affecting ~466 million people worldwide, with excessive exposure to loud noise as a leading cause. Epidemiological studies have identified hearing loss as a major risk factor for age-related cognitive decline; however, the brain regions mediating the link between the two remain elusive. Although previous studies have reported molecular changes in the hippocampus and striatum following noise exposure, it is unknown whether such changes contribute to cognitive decline associated with noise-induced hearing loss. To that end, we noise-exposed 6-month old rats, and then assessed their hearing and cognitive function at 7, 10 and 13 months of age. Rats underwent cognitive testing on the Morris water maze to assess hippocampal-dependent learning and memory, and on a striatal-dependent visuomotor associative learning task. Consistent with human studies, noise exposure resulted in mild, high-frequency hearing loss. The noise-exposed rats did not exhibit significant deficits in striatal-dependent visuomotor associative learning, yet they had a faster reaction time compared to the sham-exposed rats. Moreover, a subset of noise-exposed older rats demonstrated hippocampal-dependent spatial learning deficits, suggesting that some animals are more vulnerable to the effects of noise exposure with age. Ultimately, these novel findings expand our understanding of how brain regions outside of the auditory pathway are affected by noise exposure; findings that should be considered when investigating the link between hearing loss and cognitive decline.

2-F-272: The lateral orbitofrontal cortex consistently regulates learning from overexpectation of fear.

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The ability to alter previously established behaviours is key for survival. Two ways in which reductions in conditioned behaviours can be achieved is through overexpectation and extinction. In both cases the expected outcome, be it aversive or appetitive, is greater than that delivered, thus generating a negative prediction error and downregulating established expectations. In overexpectation, the expectation of the outcome is manipulated by inflating it through summation, whereas in extinction it is outcome delivery that is manipulated by omitting it altogether. Our previous work showed that the lateral orbitofrontal cortex (lOFC) is critical for learning from overexpectation but less so in learning from extinction. When studying the effects of lOFC function on extinction, we found a mild effect of lOFC inactivation only in initial but not subsequent extinction learning. This albeit mild effect led us to assess the generality of the role of the lOFC in overexpectation by studying the order of learning episodes. Specifically, we examined the effect of lOFC inactivation on learning from overexpectation in animals that have undergone either initial extinction or overexpectation training with a different cue. Our findings confirm that inactivation of the lOFC prior to compound training in overexpectation disrupted the reduction in responding seen on test, regardless of the order of learning and prior experience. Additionally, silencing the lOFC only resulted in a mild impairment in initial extinction. Together, these results extend and replicate

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our prior work to provide additional evidence that the lOFC consistently regulates the reduction of learned fear responses driven by overexpectation.

2-F-273: Sex-specific effects of chronic stress on intestinal permeability and depression-like behaviors

Ellen Doney[1], Laurence Dion-Albert[1], François Coulombe-Rozon[2], Katarzyna Dudek[1], Fernanda Neutzling-Kaufmann[2], Natasha Osborne[3], Joanna Kasia Szyszkowicz[4], Manon Lebel[1], Marie-Claude Audet[3], Caroline Ménard[1]

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Chronic stress, the main environmental risk factor for major depressive disorder (MDD) is linked to intestinal barrier deterioration via gut-brain signaling in gastrointestinal disorders. MDD shows high comorbidity with gastrointestinal disorders including patterns of microbiome dysbiosis and inflammatory peripheral markers, suggesting increased intestinal permeability in these patients. We investigate how the effects of chronic stress can influence manifestations of intestinal permeability in both male and female mouse models of depression. The prevalence of MDD is two-fold higher in women, however, chronic social defeat stress (CSDS) experiments have been conducted exclusively in male mice. We hypothesize that stress induces changes to gut barrier integrity in a sex-specific manner, playing a role in vulnerability or resilience. Accordingly, mice were subjected to various stress paradigms: 6-day or 28-day chronic variable stress, or 10-day CSDS. 16S rRNA sequencing assessed microbial populations pre- and post-stress. Gene and protein expression analysis of tight junctions from intestinal tissues shows alterations related to the type and duration of stress with sex-specific effects. Furthermore, CSDS induces changes in tight junction expression associated with resilience or susceptibility to chronic social stress, corresponding to phenotype severity. Our results provide evidence for the effects of chronic stress in disrupting intestinal barrier homeostasis in conjunction with the manifestation of depression-like behaviours.

G - Novel Methods and Technology Development

2-G-274: PSYCO:Py-based SYstem for Chronic monitoring of rOdent Species, an open-sourced python based system for homecage mouse tracking and image processing

Tony Fong[1], Murphy Timothy[1]

[1]University of British Columbia

We present the Py-based SYstem for Chronic monitoring of rOdent SpeciesPy-(PSYCO) Mouse Tracker (PNMT): an affordable, open-sourced, and customizable/scalable behavior recording software for small foot-print Raspberry Pi-based acquisition computers and subsequent offline analysis tools capable of recording and tracking multiple mice for extended periods of time, respectively. Video tracking coupled with radio frequency identification (RFID) was employed to track multiple mice in a modified home-cage setting for up to four days. Video and RFID recordings were completed utilizing a Raspberry Pi 3B+ or

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Pi4 micro-computer. During offline analysis performed on a PCdesktop computers, mice were tracked using You Only Look Once version 4 (Yolov4) algorithm coupled with the Simple Online and Realtime Tracking (SORT) for mice tracking, respectively. RFID readings recorded in the system were then associated with the best-matched mouse that was tracked. For evaluation, PMTNMT performance was compared to a human manual validation of video recordings containing one to four mice. PMTNMT maintained a minimum of 70% identities tracked among mice detected with an overall accuracy >above 90 %. Moreover, we also showed that PMTNMT can be adapted to other behavior apparatus such as an open field like arena or sociability chamber to track mice. Furthermore, the PSYCO tracker can incorporate inputs from popular open-sourced packages such as Deeplabcut and Traja for postures estimation and travel trajectory analysis, respectively. Overall, our group demonstrated the performance of a newly developed multiple animal tracking system capable of tracking mice for extended periods of time and adaptable to the use case of individual investigators.

2-G-275: Optogenetics defines the effects of multiple sclerosis-associated hnRNPA1 mutations on hnRNPA1 dynamics and stress granule formation.

Joseph-Patrick Clarke[1], Patricia Thibault[2], Hannah Salapa[2], David Kim[2], Catherine Hutchinson[2], Michael Levin[2]

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Evidence indicates that neurodegeneration (NDG) is a prominent feature and the primary cause of disability in multiple sclerosis (MS). Yet, knowledge of the molecular mechanisms of NDG in MS, as well as treatment options for NDG are lacking. Published data from our lab indicates that dysfunction of the RNA binding protein heterogeneous ribonucleoprotein A1 (A1) may contribute to MS pathogenesis. Therefore, to examine A1 dysfunction, we utilized an in vitro, blue light (BL) induced, optogenetic protein self-association expression system containing the optogene Cryptochrome 2 and a fluorescent mCherry reporter, to examine the effects of MS-associated somatic A1 mutations (P275S and F281L) on A1 localization, cluster kinetics and stress granule (SG) formation in real-time. Using BL stimulation followed by a period of recovery, which promotes protein self-association and dissociation dynamics (imitating a cell stress event that occurs during MS relapse), revealed that A1 mutations caused cytoplasmic mislocalization, and significantly altered the kinetics of A1 cluster formation/dissociation, and the quantity and size of clusters. Additionally, mutant A1 protein clustering also caused SG formation to occur more quickly and frequently in response to BL stimulation. Overall, this study establishes a live cell optogenetic imaging system to probe localization and association dynamics of A1. It also demonstrates that somatic mutations in A1 alter its function and promote SG formation, which supports the hypothesis that A1 dysfunction may exacerbate NDG in MS.

2-G-276: Novel method for intracerebroventricular injection in neonatal mice

Katherine Gray[1], Jordan Hamden[1], Hitasha Bajaj[1], Michael Li[1], Melody Salehzadeh[1], Shelly McErlane[1], Kiran Soma[1]

[1]University of British Columbia

Early-life stress (ELS) has profound and enduring effects on cognition and behaviour. Stressors activate the hypothalamic-pituitary-adrenal axis and increase glucocorticoid (GC) levels. GCs are important for neurodevelopment; however, high GC levels increase neuron

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death and dendritic atrophy. Rodent models of ELS use stressors such as maternal deprivation, limited bedding and nesting material, and endotoxin exposure. Alternatively, some ELS studies administer corticosterone systemically (p.o., i.p. or s.c.) to neonatal rodents. No studies have administered corticosterone in vivo directly to the neonatal brain. Here, we developed a simple and robust method to administer corticosterone to the neonatal mouse brain by intracerebroventricular (icv) injection into the lateral ventricle. We applied a local analgesic to the scalp of postnatal day 5 (PND5) C57BL/6J mice. We then delivered 2 uL of 5, 10, 15, or 45 ng/uL solutions of corticosterone with a single icv injection. 2uL of sterile saline was injected as a vehicle control. After 2.5 hr, we collected the brain, whole blood, and liver. Corticosterone levels in microdissected brain regions, blood, and liver were measured via liquid chromatography tandem mass spectrometry (LC-MS/MS). With higher doses of corticosterone, brain corticosterone levels rose accordingly while peripheral corticosterone levels did not. Our study outlines a novel paradigm of injecting corticosterone into the brain of non-anesthetized PND5 mice that can be used to elucidate the impact of locally elevated corticosterone in the brain and model ELS.

2-G-277: Hippocampal stroke in awake and freely behaving mice reveals an acute increase in exploratory behaviour time-locked to the onset of neuronal calcium dysregulation

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[1]University of Calgary, [2]Federal University of Espirito Santo, [3]Hotchkiss Brain Institute, University of Calgary

Stroke is the leading cause of adult disability and the third-leading cause of death in Canada. Ischemic strokes, caused by a blood clot in brain vasculature, are the most common presentation. There are several murine models for the study of ischemic stroke - each with unique benefits and limitations. Some stroke models require surgical intravascular insertion of filaments to block blood flow (ie. MCAO) and thus are confounded by the neuroprotective effects of anaesthesia. Other models (ie. thromboembolic or microsphere/microbead) rely on injection of material to occlude vessels and thus induce diffuse lesions with limited reproducibility. Photothrombotic stroke uses intravascular photo-oxidation of dyes to induce a local clotting cascade and generates scalable and targeted lesions in awake mice; however, it is typically limited to the superficial cortex to allow access for laser illumination, relying on a head-fixed mouse to image peri-infarct neurons. While many human strokes appear in the cortex, subcortical strokes are also common, yet current subcortical models induce stroke at diffuse locations or induce large lesions. Here, we pair photothrombosis via fiberoptic cannula with photometry to record neuronal activity in the emerging stroke core during subcortical strokes in awake, freely behaving Thy1-GCaMP6f mice. Both calcium dysregulation and lesion size scale with duration and intensity of laser illumination. Following unilateral photothrombosis in the hippocampus, mice increase both cage exploration and motility time-locked to the onset of neuronal calcium dysregulation. This model triggers a scalable subcortical lesion, while concurrently recording neuronal activity in a freely behaving mouse and translates across brain regions and diverse biosensors.

2-G-278: Development of an automated detection system for probing novel object recognition performance in mice

Raman Abbaspour[1], Steven Connor[1]

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[1]York University

An emerging appreciation for the complexity of rodent behavioural performance requires tools capable of detecting these subtleties. Traditional approaches for quantifying rodent behaviours are subject to limitations including superficial metrics, observer bias, and low throughput analysis. Moreover, these approaches lack the flexibility required for deriving new behavioral indicators of cognitive abilities. Here, our objective was to overcome these limitations through the development of a novel analytical platform based on Machine Learning (ML). Our initial application focused on the Novel Object Recognition (NOR) task, as this is a well-established, low stress method for measuring memory in mice. NOR is performed by exposing mice to 2 objects which they freely investigate. This is followed by swapping in a novel object which mice tend to spend more time exploring as they recognize the object as novel. The total amount of time mice spent exploring the novel and familiar objects is measured and compared as an indicator for recognition memory. Using young (~3 weeks old) male and female C57BL/6 mice, the NOR task was administered and recorded. We found that our software was able to reliably identify mouse direction of movement, orientation relative to objects, and speed of movement. Our software was also able to identify subtle changes in performance of NOR that were influenced by anxiety-like (thigmotaxis) states of mice. Overall, we were able to develop a low-cost, flexible GUI for analyzing NOR performance, capable of deriving the influence of anxiety on memory.

2-G-279: Rapid microcircuit mapping with 2-photon optogenetics

Christina Chou[1], Connie Guo[1], Per Jesper Sjostrom[1]

[1]McGill University

Primary visual cortex (V1) functionality is determined by its connectivity and organization. Although connectivity between pyramidal cells (PCs) has been extensively studied, interneuron (IN) connectivity remains relatively poorly explored. Here, we demonstrate a high-throughput method combining 2-photon optogenetics and whole-cell electrophysiology for cell-type specific interrogation of microcircuit connectivity. We soma-targeted the opsin ChroME to cortical PCs by injecting AAV9-CAG-DIO-ChroME-ST-P2A-H2B-mRuby3 in P1 Emx1-Cre mice. While whole-cell recording ChroME-expressing PCs in acute visual cortex slices, we used galvanometric mirrors to redirect a 1040-nm 2-photon laser beam. Spiking was reliably evoked by 5 to 7-ms-long spiral scans over the soma, but not >20 µm away. We could thus specifically drive PCs with millisecond and single-cell resolution. We next probed connectivity by patching a PC or an IN and sequentially driving candidate presynaptic PCs in a 300 µm x 300 µm field of view (FOV). Postsynaptic cell type was verified by 3D morphometry and intrinsic properties. To measure connectivity within and across layers, we investigated multiple FOVs around the patched cell. PCs connected more often to basket cells (BCs) than to Martinotti cells (MCs) or PCs (BC: 42% ± 2%; MC: 10% ± 2%; PC: 14% ± 3%; BC vs MC: $p<0.001$; BC vs PC: $p<0.001$; PC vs MC: $p=0.4$), in agreement with prior studies showing dense local connectivity to BCs. In conclusion, rapid cell-type-specific connectivity mapping across all cortical layers is now feasible.

2-G-280: Use of a novel olfactometer to assess behavioural and neural responses to odour stimuli

Filip Kosel[1], Tamara Franklin[1]

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[1]*Dalhousie University*

Identification of chemical signals is critical for survival in animals, and olfaction is key for chemosensing in mammals. Odour stimuli play a role in memory and identification of potentially harmful substances, and several species--including dogs, cats, and rodents--use olfactory cues in urine to identify potential mates, intruders, predators, and prey. Several methods of assessing olfaction have been developed for use with mice and rats, including the olfactory habituation/dishabituation (OHD) task--a classic paradigm to assess behavioural responses to social and non-social odour cues. However, the OHD task still relies on manual presentation of odour stimuli by researchers. Our aim was to adapt this task for use with an automated olfactometer, allowing for reduced researcher involvement during testing and increased precision of stimulus presentation. Here, we describe our design for an economical olfactometer that can be built in the lab and linked to commercial in vivo electrophysiology software. Briefly, rodents are placed in a testing chamber to which pumps deliver either odorized or clean air; timing and order of odour presentation is automated. Sessions are videorecorded for analysis of behaviour by either manual or automated scoring. The use of this novel olfactometer, which can be used in combination with neural recordings, offers improved accuracy over manual odour presentation in tasks like the OHD task, and minimizes extraneous effects of researcher interaction with the stimuli or apparatus.

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Poster Session 3

A – Development

3-A-281: Characterizing microglial influences on the development of the postnatal hypothalamic ventricular niche

Harmony Fong[1], Jessica Rosin[1], Deborah Kurrasch[1]

[1]University of Calgary

Relatively little is known about the neural stem cell (NSC) niche in the hypothalamus, but hypothalamic neural stem potential is thought to reside in tanycytes, a population of radial glia-like cells lining the third ventricle (3V). Depending on the timepoint studied, both neurons and glia have been reported as arising from tanycytes in the postnatal mouse brain. In complement, previous work in our lab has identified a subpopulation of microglia that lie adjacent to and influence NSCs along the embryonic 3V, raising the intriguing possibility that similar interactions persist postnatally. Here, we characterized the neuro/gliogenic potential of the hypothalamic niche across postnatal development, and asked whether its neural stem capacity was influenced by microglia. To start, we used the neurosphere assay to examine the proliferation, self-renewal, and multipotency of cells surrounding the mouse hypothalamic 3V at several postnatal timepoints. Primary and secondary neurospheres were readily formed by cells collected from microdissected hypothalamic ventricular zones between P2 and P21, and differentiation of primary spheres largely yielded cells expressing glial but not neuronal markers. Additionally, depletion of microglia using PLX5622 increased the number of primary and/or secondary spheres generated from P2 and P14 hypothalamic ventricular zones. These preliminary data provided further evidence for a proliferative, self-renewing, and gliogenic cell population in the postnatal hypothalamus, and suggested that these neural stem properties may be modulated by microglia.

3-A-282: The importance of calm mice: why should early life stress studies be conducted in an isolated quiet room

Aycheh Al-Chami[1], Carinna Moyes[1], Ting Ting Wang[1], Alysia Ross[1], Hongyu Sun[1]

[1]Carleton University

Various models of early life stress (ELS) emphasize housing animals in a quiet and isolated room, undisturbed by or shared with other investigators. While increased human activity in animal housing facilities is known to affect an array of animal behavioural, metabolic, and physiological functions, whether it creates a stressful environment and affects the developmental trajectory of the immature brain is unknown. Here, we present data outlining the implication for housing immature mice in regular housing (RH) as compared to a separate quiet room (SQR) on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) function during a critical period of brain development. The SQR had low traffic, was accessed by a single investigator, and housed a single rack, while the RH room was located in a high traffic area, shared by 16 investigators and staff, and housed 6 full racks. Using whole-cell patch-clamp recordings, we demonstrate that pups housed in RH show significant increases in AMPAR function in pyramidal neurons in both CA1 (p10-11)

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and layer IV auditory cortex (p12-15). Therefore, for ELS studies, considerations of traffic and noise levels should be taken when choosing animal housing. A quiet and separate room is required as additional stressors can permanently alter the maturation of glutamatergic synapses in the developing brain, potentially impacting research outcomes and subsequent interpretation.

3-A-283: The cell adhesion molecule Sdk1 shapes assembly of a retinal circuit that detects localized edges

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[1]McGill University

Nearly 50 different retinal ganglion cell (RGC) types sample the visual scene for distinct features such as motion direction or line orientation. RGC feature selectivity arises from its synapses with a specific subset of amacrine (AC) and bipolar cell (BC) types, but how their dendrites arborize and collect input from these specific subsets remains poorly understood. We developed a method that combines calcium imaging and post hoc histology that revealed a family of circuits that express the adhesion 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 on this neuron. These phenotypes were specific to S1-RGCs and were accompanied by selective deficits in their dendritic growth. We conclude that Sdk1 shapes dendrite growth and wiring to help S1-RGCs become feature selective.

3-A-284: Electrophysiological characterization of Rett Syndrome in iPSC-derived neuronal networks using computational network modeling

Kartik Pradeepan[1], Rebecca Mok[2], Gabriel Benigno[3], Julio Martinez-Trujillo[3], James Ellis[2], Lyle Muller[4]

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Rett Syndrome (RTT) is a neurodevelopmental disorder caused by a mutation in the gene MECP2. MeCP2 protein is found to be most abundant in neurons where it binds to DNA to act as an A-D global transcriptional regulator. Previous work has shown neurons with MECP2 mutations exhibited morphological and functional hypoconnectivity at a single neuron level. We hypothesized this hypoconnectivity between MECP2¬-mutant neurons will result in altered network development and function. Excitatory neurons derived from iPSCs from a RTT patient, two control patients, and isogenic pairs were generated. Neurons were plated on a multielectrode array and electrophysiology was measured over 6 weeks. Spatiotemporal analyses were used to quantify the electrophysiological features and computational network modeling was used to explore mechanisms driving the differences seen in vitro. iPSC-derived cultures exhibited bursting patterns that went from sparse firing to asynchronous bursting to synchronous bursting across development - quantified through burst frequency. As neuronal cultures developed, mutants grew increasingly different in their burst frequency compared to isogenic controls. Spiking network modelling revealed adaptation currents had the greatest influence on bursting. As adaptation currents increased, the burst frequency shifted to lower values. Simulated knockout experiments supported

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these results. This suggest that RTT networks may be mediated by adaptation currents, and various regulators for channels involved in adaptation may be implicated as downstream targets of MeCP2.

3-A-285: Purinergic signalling is altered in the Fmr1-KO mouse hippocampus

Matthew Napier[1], Angela Scott[1]

[1]McMaster University

Fragile-X syndrome (FXS), the leading genetic cause of intellectual disability, occurs when the Fmr1 gene on the X-chromosome is silenced, reducing the levels of Fragile-X mental retardation protein (FMRP). This loss of FMRP hinders neurodevelopment and leads to several neurological pathologies, one of which is learning and memory deficits that are attributed to dysregulated hippocampal neurogenesis. The purinergic signalling pathway, where cells use ATP and its metabolites as signalling molecules, is essential for neurogenesis but has yet to be considered in the FXS hippocampus. However, our lab has discovered abnormal purinergic signalling in the FXS cortex, suggesting FMRP regulates this pathway. We hypothesize that purinergic signalling abnormalities exist in the FXS hippocampus and contribute to the dysregulation of neurogenesis. To begin our investigation, we used the Fmr1-KO mouse model to characterize the expression of purinergic receptors known to be involved in neurogenesis. After performing Western Blots on hippocampal tissue at postnatal day 1 (P1), P7, P14, and P21, we found that the P2X7 receptor was upregulated at P7. In mice, P7 is when hippocampal neurogenesis peaks; therefore, overexpression of P2X7 at this critical time point may have increased consequences for the adult mouse. Because P2X7 can play several roles in neurogenesis, it is unclear what those long-term consequences may be. Our next step is to determine which cells overexpress the P2X7 receptor to determine which aspect(s) of neurogenesis this P2X7 overexpression may impact.

3-A-286: Sex differences in the metabolic outcomes of high-fat diet in the offspring after gestational cannabis exposure

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Based on the 2016 Survey on Drug use and Health in the USA, 4.9% of pregnant women 15-44 years old reported recent cannabis use. Studies on the long-term outcomes of gestational cannabis exposure (GCE) are limited. Although cannabis ingestion triggers short-term hyperphagia, the incidence of obesity is lower in frequent cannabis users. It is unknown whether GCE will influence the metabolic dysfunction associated with high-fat diet (HFD) consumption in adult offspring. Pregnant female mice received edible cannabis extract, equivalent to THC (5mg/kg/day) or vehicle from GD1.5 till PD10. At least 9 litters culled to 6 mice/litter from each group were examined. Daily body weight and food intake of the dams were recorded during pregnancy and lactation. Body weight and locomotor activity of the pups were monitored at several age points. Adult offspring (7 weeks old) received HFD or control diet (CD) for 12 weeks. Body weight, adiposity, glucose tolerance, insulin sensitivity, and gut microbiota composition are examined. While GCE did not alter the dams' weight gain, food intake, pregnancy duration, or litter size, it reduced the pups' body weight at PD6 and PD11, but not at later ages and decreased their locomotor activity at PD10. GCE female

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but not male offspring that received CD were more insulin resistant but not heavier or more glucose intolerant than their controls. HFD induced more insulin resistance independent of weight gain in GCE male but not female offspring. Perinatal cannabis exposure negatively impacts insulin sensitivity of adult offspring in a sex-specific manner.

3-A-287: Perinatal injury promotes a persistence of pro-inflammatory M1 phenotype in the developing brain

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Background: Extreme preterm infants are exposed to multiple inflammatory stressors over their neonatal period including perinatal cerebellar hemorrhage (CBH) and postnatal infection, known as two major risk factors for neurodevelopmental impairments. Given microglia involvement in inflammatory functions across the central nervous system, they may play a central role in the pathogenesis of cerebellar injury in developing brains. Methods: Conditional transgenic mice dependent on diphtheria toxin intracerebellar injection to deplete CX3CR1-positive cells(mononuclear phagocytes including microglial cells) were bred and exposed to CBH at postnatal day 2(P2) combined with early inflammation(LPS). Microglia phenotypic changes across time will be analyzed by flow cytometry. Results: Our preliminary data showed that prior to insult at P2, the predominant phenotype of activated microglial cells is M2 pro-repair(48,74%;n=3-6) compare to M1 pro-inflammatory phenotypes(0,88%;n=3-6) analyzed by flow cytometry from whole brain tissue(n=8-9). Two weeks after being exposed to diverse perinatal insult combinations(P15), mouse pups showed a significant change of their M1/M2 ratio compare to controls. We observed an increase of M1(7,51%;n=4-7) after LPS-exposure compare to controls(1,66%;n=4-6). We measured also a significant decrease of activated microglial cells expressing M2 phenotype from all insult groups: LPS(8,90%;n=4-7;**P=0.0025), CBH-LPS(12,53%,n=4-7,**P=0.0025) and CBH alone(26,30%,n=2) compare to controls(35,04%,n=4-6). Conclusions: Perinatal insult exposure lead to changes in M1/M2 ratio from microglial cells over time, which may translate to altered immune responses induced by future stressors exposure.

3-A-289: Role of somatostatin in regulating developmental changes of neurotransmitters in retinoic acid-induced differentiated SH-SY5Y cells

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During the dynamic process of brain development, the neurite formation and elongation are essential to establish a complex neural network in the central nervous system. Somatostatin (SST), a growth hormone inhibitory peptide, is known to play a critical role in neurotransmission, neurite formation, migration and maturation. In the present study, we examined the time-dependent (at day 1, 3, 5 and 7) developmental changes in the expression of crucial marker that govern the functional activity of neurons, including SST, choline acetyltransferase, and tyrosine hydroxylase, brain nitric oxide synthase, GABA and synaptophysin in non-differentiated and all-trans retinoic acid (RA)-induced differentiated SH-SY5Y cells. We also determined SST-mediated modulation of subcellular distribution and expression of neurotransmitter and Synaptic markers using immunocytochemistry and

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western blot analysis. Our results suggest a distinct response of RA and SST alone or in combination in regulating different neurotransmitter markers during the transition of SH-SY5Y cells from non-neuronal entity to neuronal phenotype. Here we present markers specific and time-dependent changes in differentiated cells when compared to non-differentiated SH-SY5Y cells. These data suggest that SST in SH-SY5Y cells might be associated with the stabilization and migration of neurotransmitter markers to neurites. Taken together, results described here support the role of SST in neurogenesis with a possible implication in neurological disease exhibiting interrupted neuronal communication and loss of cognitive function.

3-A-290: Age-related changes in retinal function in the vervet monkey

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Throughout life, the retina undergoes chemical and structural changes that ultimately result in altered functional properties. Electrophysiological testing is an objective method to functionally assess the state of the neuroretina. By using appropriate visual stimuli in the light-adapted eye, it is possible to isolate the contributions of specific cellular components to the elicited electrical response. In this study, we performed a light-adapted (30 cd m² background) flicker electroretinogram (ERG) in 36 adult vervet monkeys aged 9 to 28 years old, with no obvious signs of ocular pathology. A standard intensity light flash (2.57 cd s m²) was applied at eight different frequencies, ranging from 5 to 40 Hz. Changes in the stimulus-response characteristics were found in older individuals (21-28 years-old, N=16), when compared with recordings from younger monkeys (9-20 years-old, N=20). Specifically, a significant reduction in the averaged amplitude together with a prolonged implicit time of the b-wave was observed in older monkeys across all stimulus frequencies tested ($p<0.05$). Altogether, our findings corroborate the existent human literature, where ageing detrimentally affects photopic retinal responses. These results also highlight the potential use of non-human primates as a reliable model to study the early stages of visual processing over the lifespan. Overall, these age-dependent voltage and temporal changes might reflect ongoing pathological processes targeting the cone-bipolar subsystem.

3-A-291: Role of p75 neurotrophin receptor in cortical parvalbumin-positive GABAergic interneurons and cognitive flexibility

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Parvalbumin (PV)-GABAergic interneurons constitute the majority of interneurons in the cortex and play a key role in the function and synchronization of cortical networks. Alterations in PV-interneuron connectivity, in the medial prefrontal cortex (mPFC), have been related to psychiatric disorders. We have previously shown that the expression of the p75 neurotrophin receptor (p75NTR) regulates the time course of PV cell synapse maturation in a cell-autonomous fashion. Here, we study how p75NTR removal in postnatal PV cells affects the connectivity of PV interneurons and mPFC function in adult PV_Cre;p75NTRlox/lox mice. One important indication of PV cell maturation is the appearance of specialized extracellular

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matrix structures called perineural nets (PNNs) around the soma and primary dendrites of mature cortical PV cells. Conditional postnatal deletion of p75NTR in PV cells resulted in an increased perineural net (PNN) density and intensity around these cells, along with higher excitatory afferent and inhibitory efferent connectivity in PFC. These mice also showed deficits in attentional set-shifting task, a measure of attention and cognitive flexibility in mPFC, and in extinction of fear memories, both of which rely on mPFC function. Finally, we investigate whether the overexpression of P75NTR in mPFC of adult cKO can rescue PV cell structural deficit. Using a Cre-dependent adeno-associated virus, we observed a significant decrease in PV cell inhibitory efferent connectivity. Analysis on the PNN density and intensity around PV cell somata is currently ongoing. These findings uncover P75NTR as a critical regulator of PV circuit refinement and plasticity in adult PFC by simultaneously controlling PV cellular connectivity underlying cognitive function.

3-A-292: The role of Cadherin 4 in retinal circuit assembly

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Layered patterns of connectivity are a hallmark of neural circuits in the central nervous system and bring the axons and dendrites of synaptic partners into close enough proximity to synapse. In the retina, a multi-layered neuropil called the inner plexiform layer (IPL) organizes the processes of ~30 types of retinal ganglion cells (RGCs) and ~100 types of interneurons, promoting specific wiring patterns that create feature-detecting neural circuits. How retinal neurons target appropriate layers and wire specifically remains poorly understood. Here, we focus on the role of Cadherin 4 (Cdh4) in the laminar choices of developing retinal neurons. Genetic and histological studies revealed that Cdh4 labels amacrine cells (ACs) and RGCs that project to IPL sublayers containing the axons of bipolar cells that respond to light offset (OFF-BCs). Two-photon calcium imaging of Cdh4 RGCs (C4RGCs) expressing genetically encoded calcium indicators (GCaMP6f) while presenting visual stimuli show that C4RGCs comprise at least 6 OFF-RGC types. Deletion of Cdh4 causes a subset of C4RGCs to switch from OFF- to ON-responding and viral labeling studies show many Cdh4-null C4RGCs mistarget and grow in IPL sublayers where ON-BC axons reside. Next, we will match C4RGCs to molecularly defined cell types and misexpress Cdh4 to see if it can direct neurons to OFF IPL sublamina. Taken together, our results show that Cdh4 is required for a subset of RGCs to target OFF IPL sublamina and develop visual responses, suggesting that Cdh4 expression may impart positional information to developing RGCs.

3-A-293: Long-range instructive axon guidance function for netrin-1

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Gradients of secreted long-range attractants and repellents are proposed to guide growing axons during development. Netrin-1 is highly expressed by cells in the ventral ventricular zone and floor plate of the embryonic spinal cord and is essential for commissural axon

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extension to the ventral midline. It remains unclear, however, to what extent netrin-1 protein functions as a long-range or short-range cue, nor has the permissive verses instructive significance of the gradient of netrin-1 protein in vivo been identified. Here, we address how the distribution of netrin-1 protein in the developing spinal cord influences axon guidance. In early embryonic chick spinal cord, netrin-1 is expressed only by floor plate cells, yet a gradient of netrin-1 protein extends ~ 200 µm dorsal of the floor plate, exemplary of a long-range cue. In the embryonic mouse spinal cord, we show that genetic reduction of the amount of netrin-1 expressed reduces the steepness of the gradient and results in a graded severity of axon guidance defects at the ventral midline. Selective deletion of netrin-1 from floor plate cells results in loss of netrin-1 protein within ~ 200 µm of the midline, and within the same distance, flattening of the gradient and altered commissural axon trajectories. In gain-of-function assays, we demonstrate that manipulating the distribution of netrin-1 with ectopic protein expression in the embryonic spinal cord is sufficient to redirect commissural axon extension. Our findings indicate that netrin-1 secreted by floor plate cells is distributed as a long-range axon guidance cue, and demonstrate that the precise distribution of netrin-1 protein is critical to direct commissural axon extension in the embryonic spinal cord.

3-A-294: Topographic map formation and the effects of NMDA receptor blockade in the developing Xenopus retinotectal system

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Topographic organization is commonly found in the sensory systems of vertebrates. Functional topographic maps are believed to follow a developmental progression from initially coarse to more precise through an activity-dependent refinement process. To examine the emergence of topographic organization in the retinotectal system, we performed longitudinal visual receptive field mapping by calcium imaging in the optic tectum of GCaMP6-expressing transgenic Xenopus laevis tadpoles. At stage 42, just one day after retinal axons arrive in the optic tectum, and the earliest time point when visually evoked responses could be detected, a crude retinotopic functional map was evident. Animals were imaged over the following week at stage 45 and stage 48, during which more precise retinotopic organization was observed. Next, by microinjecting GCaMP6s mRNA into one blastomere of two-cell stage embryos, we acquired bilateral mosaic tadpoles with GCaMP6s expression in postsynaptic tectal neurons on one side of the animal and in RGC axons crossing over to the tectum on the opposite side. This allowed independent observation of retinotopic maps in the pre- and post-synaptic elements in the tectum. To examine the contribution of N-methyl-D-aspartate (NMDA) receptors to map refinement, we reared tadpoles in the NMDA receptor antagonist MK-801. MK-801-rearing did not prevent the emergence of retinotopic maps, but produced changes in overall map organization compared to untreated animals, including more discontinuous topographic gradients and altered receptive field characteristics. These results provide evidence that NMDA receptor activity is dispensable for coarse topographic ordering of retinotectal inputs, but play a part in the fine-scale refinement of the retinotectal projection.

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B - Neural Excitability, Synapses, and Glia: Cellular Mechanisms

3-B-295: Age-related LTCC and NMDAR expression in the hippocampus and olfactory cortex in rats

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Neuronal calcium is a critical mediator for learning and memory. However, with age, calcium dysregulation leads to cognitive decline. L-type calcium channels (LTCCs) and N-methyl-D-aspartate receptors (NMDARs) mediate Ca2+ influx in neurons. We hypothesize that there are age-related changes of Ca2+ channel expression in the piriform cortex (PC) and hippocampus, two areas that are crucial for olfactory and spatial learning ability. We measured synaptic and extrasynaptic levels of LTCCs (Cav1.2) and NMDAR subunits (GluN1, GluN2A, and GluN2B) in neonatal, adult, and aged rats using Western blot. PSD-95 colocalizing and non-colocalizing Cav1.2 and GluN2B expression were compared between adult and aged brains using immunohistochemistry and confocal microscopy. The expression of hippocampal synaptic, but not extrasynaptic, NMDARs was higher in adult and aged groups compared to neonates. However, GluN2A/2B ratios and synaptic:extrasynaptic ratios of NMDAR subunits were similar across age groups. Cav1.2 had higher expression in the soma of CA1 neurons in aged rats. In contrast, in the PC, GluN2A/2B and synaptic:extrasynaptic ratios were higher in adult PC compared to neonates. Extrasynaptic, PSD-95 non-colocalizing Cav1.2 expression was higher in the aged PC. Our data suggest that PC and hippocampus vary in age-related channel expression. PC maturation is accompanied by a switch from GluN2B to GluN2A subunits. Higher somatic Cav1.2 expression in CA1 and higher extrasynaptic Cav1.2 in the PC may correlate with aging-associated disruption of calcium homeostasis and cognitive decline

3-B-296: Investigating mechanisms of Wallenda/DLK axonal injury signaling restraint by spared synapses

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The integrity of a neuron's axon is fundamental for its function within a circuit, thus it is logical for nervous systems to have evolved plasticity mechanisms for reacting and adapting to axonal damage. A conserved MAP Kinase signaling pathway regulated by the DLK/MAPK12 kinase, known as Wallenda (Wnd) in Drosophila, becomes activated in damaged axons and is required for both axonal regeneration and cell death depending on the context of injury. To understand how DLK/Wnd signaling becomes activated, we have considered the role of synapses. Most paradigms of nerve injury lead to a loss of all synaptic connections made by a neuron, however depending upon the location, damage to branched axons can leave spared synapses. We probed the activation of Wnd following injuries at different locations in multiple types of branched axons in Drosophila larvae, and found that the presence of a single synaptic connection is sufficient to restrain Wnd injury signaling. In our studies, to better understand the mechanism for this restraint, we noticed that manipulations that lead to synaptic retraction also lead to activation of Wnd signaling, suggesting a connection between mechanisms that maintain synaptic integrity and the

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control of axonal injury signaling. Overall these findings point to a new cell-intrinsic mechanism that enables distinct responses to axonal damage depending upon injury location.

3-B-297: Homeostatic-like potentiation of the aversive habenulo-raphe pathway in an animal model of post-stroke depression

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Stroke is the third leading cause of death and the primary cause of adult long-term disability in Canada. Despite increasingly efficient rehabilitation programs, stroke survivors experience an unusually high incidence of depressive symptoms which, beyond the emotional suffering, also undermine recovery outcomes by reducing patient motivation levels. Human and animal studies have linked the incidence of post-stroke depression to the extent of prefrontal cortex (PFC) damage. We hypothesized that PFC stroke promotes the development of depressive phenotypes by triggering maladaptive network remodelling in mood-related networks. Both the PFC and the epithalamic lateral habenula (LHb) are limbic structures that send powerful, top-down axonal projections to the serotonergic dorsal raphe nucleus (DRN), a key neuronal hub for mood regulation. We used viral, optogenetic and electrophysiological strategies to outline the functional architecture of the PFC and LHb projections to DRN. We found that an endothelin-1-mediated stroke in PFC triggers a time-dependent upregulation of key functional features of the glutamatergic input from the LHb to DRN 5-HT neurons. Because the LHb-DRN pathway encodes emotional features such as aversion and anticipation of threat, a maladaptive, homeostatic-like upregulation of this pathway may contribute to the depressive symptomology following stroke.

3-B-298: LRRTM1 and LRRTM2 regulate synapse development and plasticity through distinct roles in developing and mature hippocampal circuits

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Neurons in the brain communicate at specialized junctions known as synapses, which are comprised of pre- and post-synaptic compartments. Synapses are highly plastic and undergo activity dependent changes in synaptic strength, a phenomenon required for learning, memory, other aspects of cognition and behavior. A class of cell-surface adhesion proteins known as synapse organizers mediates the development of synaptic connections. Leucine rich repeat transmembrane neuronal proteins (LRRTM) are postsynaptic cell adhesion molecules that promote excitatory synapse development through binding to their presynaptic receptors, neurexins. To study the role of LRRTM1 and LRRTM2 in vivo, we did a temporal knockout study where we deleted LRRTM1/2 in developing and adult brain and observed synaptic morphology, function and behavior. We studied synapse development and plasticity in hippocampal neuronal circuits through immunostaining and electrophysiology where we found that these proteins maintain morphology and plasticity in both developing and mature circuits. Further, we show that LRRTM1/2 are not required for

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these roles in dentate gyrus of developing hippocampus. Lastly, LRRTM1 and 2 are required to regulate endurance of fear memory, a memory encoded by dorsal hippocampus in both the circuits. Thus, our study shows that LRRTM1 and 2 regulate excitatory synapse development and plasticity in dorsal hippocampus of both developing and mature brain circuits with distinct mechanisms.

3-B-299: Dynamic regulation of palmitoyltransferases by synaptic activity

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The formation and remodeling of synaptic contacts require the precise distribution and trafficking of proteins to specialized compartments. This dynamic trafficking of synaptic proteins is partly controlled by S-palmitoylation, which is the most common form of post-translational lipid modification in the brain. Notably, several studies have shown that synaptic proteins can be differentially palmitoylated in response to synaptic activity. However, it is unclear how changes in synaptic activity alters protein palmitoylation. Here we show that increasing synaptic activity in primary rat hippocampal cultures using a well-established chemical LTP (cLTP) paradigm leads to post-translational modifications in ZDHHC enzymes which in turn impact enzyme stability, protein interaction and function. Notably, we observe the same post-translational modifications following the acquisition of contextual fear memory in vivo. In contrast to that observed for palmitoylating enzymes, we observed no activity-induced changes in the activity of thioesterases nor post-translational modifications of the thioesterase, ABHD17. These findings suggest that the differential palmitoylation of synaptic proteins following synaptic stimulation is mediated through post-translational modifications of ZDHHC enzymes that in turn regulate enzyme stability and function, and not through changes in depalmitoylating thioesterases.

3-B-300: Modulatory effects of endogenous orexin and dynorphin on ventral tegmental dopamine neurons of known projection targets

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Dopamine (DA) neurons in the ventral tegmental area (VTA) respond to motivationally relevant cues and are key targets of addictive drugs. VTA DA neurons receives input from lateral hypothalamic (LH) orexin/hypocretin neurons which also express and co-release the neuropeptide, dynorphin (LHox/dyn). These peptides have opposing effects on the firing activity of VTA dopamine neurons and drug-seeking behavior. Exogenous application of ox and dyn, modulates non-overlapping VTA dopaminergic projections. However, the effect of endogenous stimulation of LHox/dyn-containing projections to the VTA remains uncharacterized. This study combined circuit tracing, optogenetics and patch clamp electrophysiology to determine the effects of endogenous LHox/dyn release on dopaminergic projections to the basolateral amygdala (DA-BLA) or the medial (DA-mAcbSh) or lateral (DA-lAcbSh) of the nucleus accumbens. Photostimulation of channelrhodopsin expressed in LHox/dyn inputs in the VTA inhibited firing of most DA-BLA neurons. However, photostimulation of LHox/dyn inputs in the VTA both increased and reduced firing of DA-lAcbSh or DA-mAchSh neurons. Antagonists to ox1 (SB334687) or kappa opioid (norBNI) receptors reversed the potentiation or inhibition of firing, respectively. Finally,

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photostimulation of LHox/dyn potentiates evoked NMDA EPSCs of DA cells via Ox1 receptors. Our findings provide evidence that LHox/dyn corelease may tune the output of the VTA by simultaneously inhibiting and activating different VTA projection neurons that contribute to different aspects of reward seeking. Keywords: orexin, dynorphin, reward, ventral tegmental area.

3-B-301: Panx1 channels promote both anti- and pro-seizure-like activities in the zebrafish via p2rx7 receptors and ATP-signalling

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The molecular determinants of excitation-inhibition imbalances promoting seizure generation in epilepsy patients are not fully understood. Experimental evidence suggests that Pannexin1 (Panx1), an ATP release channel, modulates excitability of the brain. Here, we use zebrafish larvae with Panx1a and Panx1b channels genetically knocked out or pharmacologically inhibited to evaluate the consequences of targeting Panx1 for antiepileptic drug therapies. Pentylenetetrazole was used to chemically induce seizures during in vivo recordings of local field potentials and for behavioral and molecular phenotyping. We find that loss-of-function panx1a gene mutations, or pharmacological blockade of both channels significantly reduces ictal-like events and seizure-related locomotion. Loss of panx1a also improves survival rates and transcriptome data demonstrate altered metabolic and cell signaling states. The pro- and anticonvulsant activities of both Panx1 channels affect ATP release and the purinergic receptor P2rx7. We propose that Panx1 zebrafish models offer opportunities for comprehensive studies of seizure mechanisms and for anticonvulsant drug discovery.

3-B-302: Afferent control of cholinergic interneurons in the nucleus accumbens medial shell

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Despite representing less than 1% of neurons in the nucleus accumbens (NAc), cholinergic interneurons (ChIs) exert dominant modulatory influence over the region and play a central role in guiding motivated behaviour. ChIs provide dense local innervation and are tonically active, but alter their activity patterns in response to salient stimuli and during reward learning. While the regulation of ChIs is well studied in the dorsal striatum, little is known about how they are engaged in the NAc. Multiple excitatory inputs project to the NAc, but how they target and regulate the activity of ChIs is largely unknown. We have identified the circuit and synaptic mechanisms through which long range inputs alter ChI firing in the NAc medial shell. We find that the paraventricular nucleus of the thalamus (PVT) and the ventral hippocampus (vHPC) are the main excitatory inputs to ChIs in the NAc medial shell. While the PVT activates ChIs, the vHPC strongly pauses firing, due to pronounced recruitment of feed-forward inhibition. In contrast to the dorsal striatum, this inhibition reflects strong connections from local parvalbumin interneurons onto ChIs. Our results highlight how different afferent streams operate through the local circuit to engage ChIs in the NAc medial shell, revealing fundamental differences in local connectivity.

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3-B-303: Defective integration of excitatory inputs onto the basal dendrites of layer 5 pyramidal neurons in a mouse model of Fragile X Syndrome

Diana Mitchell[1], Maxime Blanchard[1], Soledad Miranda-Rottmann[1], Sabrina Tazerart[1], Roberto Araya[1]

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Fragile X syndrome (FXS) is the most frequent form of inherited mental retardation and common known cause of autism. Defects in the processing and integration of excitatory inputs in cortical neurons likely contributes to the behavioral phenotype associated with FXS. A key function of the neocortex is to associate external sensory information with an internal representation of the world to make predictions about the future. Layer 5 (L5) pyramidal neurons integrate sensory inputs onto their basal dendrites with information from other parts of the cortex at the distal tuft dendrites. Here, we aimed to uncover how L5 pyramidal neurons from Fmr1-KO mice integrate synaptic inputs at the level of single spines in the basal dendrites. We used two-photon uncaging of caged glutamate to activate nearly simultaneously two clustered spines in L5 pyramidal neurons. We show that these excitatory inputs onto spines integrate sublinearly in Fmr1-KO mice, while those of wild-type animals summate linearly. Since FXS is characterized by several channelopathies in pyramidal cells, we are currently investigating the role of calcium-activated potassium channels in explaining the observed defects in integration. Taken together, the results from these experiments will help uncover the role of ion channels in excitatory input integration and identify novel targets for the design of specific drugs to successfully treat FXS. This work was funded by the CIHR and a FRQS postdoctoral fellowship to D.E.M.

3-B-304: Adaptive purinergic P2X7 and P2Y2 signaling following spinal cord injury in Danio rerio

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Mammalian spinal cord injury (SCI) occurs by a primary mechanical trauma that is exacerbated by a secondary cellular insult in the form of neuroinflammation, cell death, and reactive gliosis. The lack of functional recovery may be attributed to the inability of mammals to replace lost neurons. In zebrafish (Danio rerio), the secondary insult is attenuated and allows for the development of a spinal microenvironment that fosters regeneration. Radial glia lining the zebrafish central canal undergo injury-induced proliferation and neuronal differentiation, yet the molecular mechanisms that underlie these processes remain elusive. Previous reports have identified roles for purinergic P2Y2 and P2X7 receptors in mammalian neural progenitor cell proliferation and neuronal differentiation, respectively. Given that the purinergic system is evolutionarily conserved among vertebrates, we hypothesize that radial glia proliferation and neurogenesis following zebrafish SCI may be mediated by P2X7 and P2Y2 signaling. Preliminary immunohistochemical data suggests that radial glia express P2X7 and P2Y2 receptors. Preliminary Western blotting data shows significant upregulation of P2Y2 receptor expression at 1 day following zebrafish SCI, as well as significant downregulation of P2X7 receptor expression at 7 days. This contrasts the more gradual increase in P2Y2 receptor expression as well as the general increase in P2X7 receptor expression following mammalian SCI. Specific blockers for P2X7 and P2Y2 will be used to ascertain the roles of these receptors in the zebrafish SCI response. This work is well suited

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to advance our current understanding of successful central nervous system regeneration and elucidate the signaling pathways involved.

3-B-305: Sustained activation of awake mouse neocortex unleashes an astrocyte-mediated amplification of neurovascular coupling

Adam Institoris[1], Milène Vandal[2], Govind Peringod[2], Cam Ha Tran[3], Xinzhu Yu[4], Cheryl Breiteneder[1], Leonardo Molina[2], Baljit Khakh[5], Minh Dang Nguyen[1], Roger Thompson[1], Grant Gordon[1]

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Investigating cerebral blood flow (CBF) at the cellular level in awake animals has come of age and CBF enhancement to neural activation - termed functional hyperemia - reveals a biphasic profile, suggesting temporally distinct components that have not been thoroughly explored. At the same time, evidence casts doubt on the role of astrocytes in functional hyperemia, but the possibility exists these cells contribute within a select temporal window during brain activation which is more readily observed in the awake state. Using two-photon microscopy in awake mice, we show that clamping astrocyte Ca2+ signaling in vivo reduces sustained but not brief sensory-evoked arteriole dilation. Chemogenetic activation of astrocytes selectively augments sustained hyperemia. NMDA-receptors and epoxyeicosatrienoic acid explain the astrocyte-mediated effects on the late, escalating phase of functional hyperemia but do not contribute to brief increases in CBF. We propose that a fundamental role of astrocyte Ca2+ is to amplify the late component of functional hyperemia when neuronal activation is prolonged.

3-B-306: A serotonergic recurrent inhibitory network filters threat information over behavioral timescales

Michael Lynn[1], Sean Geddes[1], Mohamad Chahrour[1], Sebastien Maillé[1], Emerson Harkin[1], Erik Harvey-Girard[1], Samir Haj-Dahmane[2], Richard Naud[1], Jean-Claude Béïque[1]

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The habenulo-raphe pathway is implicated in orchestrating optimal behavioral responses to aversive, threatening or stressful environments. Here, we consider how long-range inputs from lateral habenula (LHb) influence circuit dynamics in the dorsal raphe nucleus (DRN). We find that habenulo-raphe afferents triggered classical monosynaptic excitation of 5-HT neurons, as well as strong disynaptic inhibition whose induction was steeply frequency-dependent and which persisted for seconds. This novel inhibition was mediated by a GIRK conductance activated by 5-HT1A receptors. Optogenetic and pharmacological manipulations in DRN revealed, unexpectedly, that 5-HT neurons are organized in a recurrent inhibitory network, refuting the classical model of autocrine activation of 5-HT1A autoreceptors. Electrical stimulation approaches revealed that these inhibitory connections exhibited robust, dramatic short-term facilitation that we formalized with a linear-nonlinear plasticity model. Using experimentally-constrained network models, we found that excitatory inputs led to paradoxical serotonergic inhibition at high frequencies, and this polarity switch was dependent on plasticity dynamics and not on recurrent inhibition itself. To test the

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physiological relevance of this computation for processing threat information from the LHb, we developed a simple auditory classical conditioning paradigm and tested key predictions of our model through in vivo optogenetics. Notably, stimulating the habenulo-raphe pathway at high frequencies, but not at low frequencies, depressed goal-directed anticipatory licking behavior. We suggest that the computation sustained by this circuit motif categorizes synaptic inputs to implement optimal adaption of behavioural policies in threatening environments.

3-B-307: Cell-type specific modulation of network-wide functional connectivity

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In the prefrontal cortex (PFC), an elaborated repertoire of activity arises from the interaction of excitatory (E) and inhibitory (I) neurons organized in stereotyped connectivity motifs. It still remains, however, unclear how different classes of neurons contribute to functional connectivity - the pattern of pairwise correlations between populations of neurons - at the scale of local cortical networks. To examine the contribution of neuronal subtypes to cortical dynamics, we used in vitro recordings of PFC circuits and computational modeling. We recorded and stimulated spiking activity in acute slices of PFC by combining electrophysiological and optogenetic methods on multi-electrode arrays containing 4,096 electrodes. To parse out the contribution of distinct cell types, we developed a spike sorting technique to distinguish excitatory neurons from inhibitory interneurons. Our sorting algorithm was validated using a combination of viral and optogenetic strategies to activate parvalbumin (PV) cells. We found that optogenetically activating PV neurons led to a counter-intuitive increase in excitatory pyramidal activity and a decrease in overall inhibition. To understand how the functional connectivity of these cortical ensembles could yield such a network response, we developed an integrate-and-fire model of somatostatin, parvalbumin and pyramidal cell populations that captured these effects. The model relied on a strong tonic activation of PV cells and a precisely balanced connectivity onto individual excitatory cells. Altogether, the results from this experimental and computational study begin to highlight rich, and at times counter-intuitive, network responses that emerge from the complex and dynamical mapping between the various cortical E and I cell ensembles.

3-B-308: Atypical subiculum pyramidal neurons form dedicated projections and exhibit morphological and electrophysiological differences

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Subiculum pyramidal neurons form the main output of the hippocampus, and are classically viewed as giving rise to memory by branched structures that receive proximal and distal input. Here, we identified a sparse pyramidal cell subpopulation within the subiculum that diverges from classical pyramidal neuron characteristics across connectivity, morphology, and intrinsic activity. Via transcriptomics, we identified a sparse excitatory neuron population that occupies the deepest layer of the subiculum, and generated a new transgenic mouse line that allows cre-mediated cell-type-specific access of these deep cells. Combining this transgenic line with cell-type-specific viral tracing tools, we discovered that this deep cell population forms dedicated projections to the anterior thalamic nuclei, a key brain region in

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spatial working memory. Moreover, these deep cells lack radial oblique dendrites typical of classical subiculum pyramidal cells. Motivated by this unique local and long-range structure of these cells, we investigated potential differences in intrinsic function via whole cell patch-clamp recordings. Recording results revealed that these deep cells exhibited an increased input resistance compared to classical pyramidal cells in the subiculum. Altogether, our data provides evidence for a previously unknown subiculum pyramidal cell subtype that exhibits unique structural and intrinsic characteristics, which could indicate a potentially specialized role in spatial memory. Future work will be integral to identifying the functional correlates of this atypical population.

3-B-309: Synaptopodin, a novel actin-associated protein, plays important role in mGluR-LTD

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Synaptic plasticity, characterized by long-term potentiation(LTP) and long-term depression (LTD), is an important physiological phenomenon that is thought to underlie the mechanism of learning and memory formation. Dysregulation in synaptic plasticity is associated with various neurological disorders. Successful treatments to enhance learning have been hard to target to the lack of understanding in the mechanisms underlying synaptic plasticity. Synaptopodin (SP), a novel actin-associated protein, was found to be an important regulator of synaptic plasticity and learning. SP is found in a subset of dendritic spines, namely the larger, functionally stronger synapses. It is associated with an intracellular organelle the spine apparatus which is responsible for calcium release from internal calcium stores and local protein synthesis. Previous research demonstrated that SP knock-out (SPKO) mice have impaired NMDA- dependent LTP and spatial learning ability but no change in NMDA-dependent LTD. mGluR-LTD is another form of LTD in the hippocampus and its expression mechanisms are much less understood than NMDA-LTD. mGluR-LTD requires IP3R-dependent calcium signaling and protein synthesis-dependent pathway. Its dysregulation has been associated with learning deficit in many neurological diseases, in particular, Fragile X syndrome, the most prevalent neurodevelopmental disorder. Using SPKO mice, we found a reduction in mGluR-LTD compared to wildtype mice. We report that mGluR-LTD - through activation of mGluR1 but not mGluR5 - drives selective loss of the larger more stable excitatory synapses distinguished by the lack of SP. We also observed a signifcant reduction of IP3R in SPKO spines. These findings identify spines that harbor SP as the cellular locus of mGluR-LTD.

3-B-310: Study of the mechanisms involved in the remodeling of the actin cytoskeleton induced by Latrophyllins 1,2 and 3

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Latrophyllins belong to the family of adhesion G protein-coupled receptors, capable of binding to actin-associated scaffold proteins. They are expressed in various tissues, suggesting that they might participate in biological processes that are ubiquitous. Here we focus on actin cytoskeleton dynamics to explore the role of latrophilins in mammalian cells. Overexpression of each latrophilin isoform comparably increased cell volume while

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modifying the net profile of F-actin-dependent cell structures, as evaluated by confocal microscopy analysis. Latrophilin deletion mutants evidenced that direct coupling to the intracellular machinery was a requirement for modulating cell structures. The association between latrophilins and the actin cytoskeleton was detected by co-immunoprecipitation assays and corroborated with immunocytochemistry analysis. Consistent with the destabilization of F-actin structures, latrophilin isoforms constitutively induced a prominent increase in the activity of actin depolymerizing factor, cofilin, evaluated by western blot assays. Intercellular adhesion events stabilized by heterophilic Teneurin-4 trans-interactions disrupted latrophilin colocalization with F-actin and led to an isoform-specific rescue of cell extensions. Therefore, we found that constitutive signaling of latrophyllins and their activation by ligand directly involves the actin cytoskeleton machinery

3-B-311: The effects of aging on intrinsic properties of pyramidal neurons in the piriform cortex and hippocampus

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Aging is associated with cognitive decline and memory loss in humans. In rats, age-associated impairment of spatial and olfactory learning has been observed. We investigated how neuronal excitability changes during aging both in pyramidal neurons of the piriform cortex (PC) and in the CA1 layer of the hippocampus, two key areas involved in these behaviors. In young (<5 months old) and aging Sprague-Dawley rats (>18 months old), we used whole-cell patch clamp recording to measure intrinsic electrophysiological properties of pyramidal neurons in each region. To preserve the health of slices, rats were intracardially perfused with cold and bubbled (95% O2, 5% CO2) artificial cerebrospinal fluid prior to dissection and slicing. Sagittal slices were incubated in N-methyl-D-glucamine (NMDG)-based recovery solution for 10 minutes, and then transferred to a HEPES buffered holding solution for full recovery. In whole-cell configuration, cells were injected with depolarizing currents to generate a current-voltage (I-V) relationship, where somatic and action potential (AP) properties were measured. In addition, current was injected to characterize slow afterhyperpolarization (AHP). In both regions, AP threshold was significantly higher for aged rats, with larger fast AHP. Aged hippocampal neurons also displayed a reduced excitability, along with higher input resistance and a significantly larger slow AHP. These differences in intrinsic neuronal function may contribute to underlying age-related mechanisms of reduced synaptic plasticity and overall cognitive decline.

3-B-312: The effects of choline on hippocampal synaptic plasticity following prenatal ethanol exposure.

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Prenatal ethanol exposure (PNEE) results in lifelong cognitive difficulties, with notable impairments in learning and memory. Although there is no treatment, current research is exploring the essential nutrient choline to improve cognitive outcomes. However, little is known on how choline supplementation alters synaptic plasticity or how cholinergic circuits are disrupted following PNEE. We utilized a first two trimester-equivalent PNEE model and examined changes in offspring synaptic plasticity. (1) In vitro electrophysiology experiments

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were conducted at postnatal day (P) 21-28. Acute choline exposure caused a long-term depression of fEPSP slope in the medial perforant pathway of the dentate gyrus (DG) which was dependent on M1 ACh receptors. PNEE offspring had a greater immediate depression and a unique involvement of NMDA receptors. (2) In a second set of experiments, offspring were treated with either choline chloride or a saline control from P10-30 and analyzed at P31-35 or P60-90. High frequency stimulation (50 pulses @ 100 Hz repeated 4x) was used to determine changes in long term potentiation (LTP). PNEE decreased the magnitude of LTP in male, but not female, juvenile offspring which postnatal choline supplementation increased. However the long-term effects of choline supplementation may be through the alteration of the LTP threshold. These data indicate that (1) PNEE alters cholinergic signaling within the DG and (2) postnatal choline supplementation has long-lasting impacts on synaptic plasticity which may convey benefits for improved learning and memory outcomes.

3-B-313: Ketamine-induced neurotoxicity mediated through endoplasmic reticulum stress

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There is growing concern over the increased use of ketamine in recreational and therapeutic settings due to potential toxic effects. Recent studies have demonstrated that ketamine is cytotoxic in several cell lines, such as on nephrons, hepatocytes, and hippocampal cells. Ketamine has been shown to dysregulate the mitochondria and increase ROS production and DNA fragmentation leading to apoptosis. What remains unclear is the effects of ketamine on endoplasmic reticulum (ER) stress in striatal neurons. Perturbations to ER homeostasis, such as calcium dysregulation, can initiate ER-mediated cell death and is associated with neurodegeneration. Thus, we aimed to examine whether ketamine is neurotoxic through ER stress induction. Mouse striatal cells were treated with ketamine (10uM, 100uM, 1mM) for 12 to 72 hrs. Following treatment, intracellular Ca2+ was measured using fluorescence, and changes in ER genes were examined using RT-qPCR. After 24 hrs, 1mM ketamine was toxic to striatal cells, as demonstrated by a time-dependent decrease in cell viability compared to controls. Within 12 hrs, ketamine sustainably reduced intracellular Ca2+ levels and induced UPR activation that favoured pro-apoptotic signalling over cell survival. Upregulation of GRP78, the master regulator of ER stress, was observed up to 24 hrs, while prolonged exposure decreased expression. Further, upregulation of pro-apoptotic UPR protein CHOP was shown throughout the experiment. Together, these findings demonstrate that ketamine-induced neurotoxicity is partially mediated through ER stress-induced apoptosis.

3-B-314: Visually-evoked calcium transients in glia are mediated by sodium-calcium exchangers in the developing retinotectal system

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Despite demonstrations that a number of different types of sensory stimuli can evoke calcium responses in glia, a comprehensive understanding of the mechanisms underlying the generation of these events in intact animals remains limited. To thoroughly investigate the signalling pathways mediating the recruitment of glial activation during visual stimulation, we generated Xenopus laevis tadpoles which express GCaMP6s in all cells of the brain and

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used in vivo two-photon microscopy to simultaneously image both neurons and glia in the developing retinotectal system of intact animals. Using a systematic combination of visual stimulation and pharmacological manipulation during live imaging, we were able to demonstrate that radial astrocytes in the optic tectum are highly responsive to visual stimulation, and that visually-evoked responses in these glia continue to occur following broad blockade of all glutamate receptors and the subsequent silencing of post- but not pre-synaptic neuronal activity. We observed that visually-evoked responses in radial astrocytes are silenced following the additional blockade of either glutamate transporters or sodium-calcium exchangers (NCX) and that the blockade of NCX alone is sufficient to prevent radial astrocytes from responding to visual stimulation, suggesting NCX may play a pivotal role in glia during early development of the visual system.

3-B-315: The involvement of the locus coeruleus in valence signalling: An interaction between activation mode and downstream receptor heterogeneity

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The locus coeruleus (LC) releases brain-wide norepinephrine (NE) in response to arousing stimuli to modulate attention, perception, and learning and memory. Recent work shows that phasic and high tonic LC activity signal positive and negative valence, respectively. How does global LC activity result in specific effects? Evidence suggests that these two modes differentially activate target structures. The basolateral amygdala (BLA) is involved in positive and negative valence. We hypothesized that phasic and tonic LC activity would bias activation towards the nucleus accumbens (NAc)- and central amygdala (CeA)-projectors of the BLA respectively. Adult tyrosine hydroxylase-Cre rats received infusions of a light-sensitive ion channel (AAV-DJ-EF1a-hChR2(H134R)-mCherry) and optic cannula in the LC, and retrograde tracer cholera toxin subunit-B (CTB) in the NAc and CeA for BLA labelling. Rats received phasic (10Hz, 300 msec every 2 sec), tonic (25Hz), or no stimulation in the presence of an odor. The BLA underwent immunohistochemistry and was imaged for cFos and CTB co-expression. Phasic and tonic LC stimulation biased activation towards BLA NAc- and CeA-projectors respectively. LC simulation led to greater activation of the VTA and VTA NAc-projectors than other groups. Preliminary data provide a mechanistic insight that alpha-1 and Beta-2 adrenoceptors are preferentially expressed on NAc-projectors of the BLA. This work is furthering our understanding of the mechanisms underlying the firing mode-specific functions of the LC.

3-B-317: Functionally distinct astrocyte calcium signaling in response to vasoconstriction

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Astrocytes have emerged as crucial players in the regulation of synaptic and microvascular physiology as they possess unique phenotypic features that allow for dynamic responses to changes in brain homeostasis. One of the hallmarks of the astrocyte response is the generation of variety of different calcium transients, which gate downstream cellular processes that regulate both synaptic efficacy arteriole diameter to coordinate oxygen

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deliverywith the metabolic demand of the neural tissue. Recent findings demonstrate that astrocyte peri-vascular endfoot calcium transients occur via stretch-mediated TRPV4 channels in response to increases in vessel tone. It is currently unknown though, how astrocyte microdomain calcium transients in the astrocyte arbor, distal to the vasculature and endfeet, are impacted by changes in vessel tone. Additionally, it is unknown how putative changes in blood supply, and thus calcium signalling, influence the ability of astrocytes to release gliotransmitter onto synapses such as ATP or D-serine. Using both a membrane tethered astrocyte GCaMP mouse line (Aldh1l1 - Cre/ERT2 x lck-GCaMP6) and a cytosolic astrocyte GCaMP mouse line (Aldh1l1 - Cre/ERT2 x AI148), we observed calcium transients in response to vasoconstriction. We demonstrate that constriction of the vessel in response to U46619 leads to an increase in calcium event frequency, amplitude and area in astrocyte endfeet. However, in the distal arbour of the astrocytes, microdomain calcium events decreased in size, amplitude, and frequency. These data show that the astrocyte arbor and endfeet exhibit distinct Ca2+ responses to arteriole tone, suggesting functionally distinct role at the vessel vs the synapse.

C - Disorders of the Nervous System

3-C-318: Oxidative stress-related genes are differentially expressed in neurons of an Alzheimer's disease rat model

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Rationale: Oxidative stress is implicated in Alzheimer's disease (AD) as well as other neurodegenerative diseases. Furthermore, oxidative damage markers that represent protein, DNA, and lipid oxidation, are elevated at late disease stages in animal models of AD and in the brains of individuals with mild cognitive impairment and AD. However, the earliest role of oxidative stress during the pre-plaque AD pathology remains unknown. This study aims to investigate oxidative stress-related gene expression in amyloid β-burdened neurons at early, pre-plaque stages in a transgenic (Tg) rat model of the AD-like amyloid pathology. Methods: Laser capture microdissection was used to excise CA1 and subiculum hippocampal neurons from 5-month old (pre-plaque) wild type (Wt) and Tg McGill-R-Thy1-APP rats. RNA from these neurons was isolated and the expression of 84 oxidative stress-related genes was assessed by qRT-PCR. To assess changes at the protein level, immunofluorescence microscopy was used. Results: Aβ-burdened hippocampal neurons showed elevated expression of DNA repair and antioxidant genes when compared to Wt neurons. Aligning with the qRT-PCR results, at the protein level, there was an increase in the DNA repair protein XPD in Tg subiculum neurons. Conclusions: These results show that there is an early change in oxidative stress-related gene expression in Aβ-burdened hippocampal neurons at pre-plaque stages of the AD pathology. The differential expression observed in these neurons likely contributes to the subsequent oxidative stress and damage observed in AD.

3-C-319: A Drosophila model depicting Braak-like propagation of Tau pathology

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Prion-like propagation through circuits is believed to be the mechanism by which tau pathology spreads throughout the brain in tauopathies like Alzheimer's disease (AD). This is reflected in the neuropathological Braak-staging of disease and manifests in the progressive cognitive decline evident clinically. Though various synaptic players are implicated, the precise players and mechanism(s) mediating trans-cellular spread of pathological tau species remain unclear. Furthermore, though trans-cellular spread of pathological tau species has been demonstrated in many experimental models, no study has yet reported any neurobiological consequence in recipient neurons. Moreover, in all such studies, the tau species that propagates is invariably mutated or isolated from pathological fractions of brains of tauopathy patients. This is puzzling given that it is wild-type tau which becomes pathological and spreads in AD, and this process is accompanied by neurodegeneration. We report a novel Drosophila model in which wildtype human tau expressed in select neuronal subsets becomes pathological and undergoes trans-cellular spread through adult brain circuits, causing neurodegeneration reminiscent of late stages of disease in AD brain. Preliminary data indicate that this spread of pathogenic tau species is dependent upon the basal activity of recipient circuits. The superior genetic tractability of this model makes it ideally suited for dissection of the key players that mediate this pathogenic process through genetic and pharmacological modifier screens. Furthermore, the availability of functional and behavioural assays for many adult brain circuits will enable future studies to more directly reveal the neurobiological consequences of spreading tau pathology.

3-C-320: Enhancing the potassium chloride co-transporter KCC2 reverses functional deficits associated with Alzheimer's disease-related mutations in mice

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Growing evidence indicates that during early stages of Alzheimer's disease (AD) abnormal brain activity occurs due to disruption of GABAA-mediated transmission. While disrupted GABAA signaling may result from several mechanisms, recent evidence points to deficits in the potassium-chloride cotransporter KCC2, responsible for maintaining low intracellular chloride in neurons to maintain robust inhibition. In this study, we validate whether KCC2 is downregulated in two transgenic mouse lines that develop AD-like amyloid-beta pathology and symptoms. Further, we examine whether by restoring KCC2 function we can alleviate deficits associated with AD. We found a decrease in the global and membrane protein levels of KCC2 in layer II/III of the prefrontal cortex of 5xFAD mice. In addition, ex vivo chloride imaging revealed impaired Cl- transport in the 5xFAD mice. Moreover, the power of hippocampal gamma oscillations was decreased in the APPNL-G-F mice, as predicted from deficits in KCC2. Consistent with this prediction, treatment with CLP290, a KCC2 activity enhancer, restored the power of the higher band gamma oscillations. Finally, short-term administration of CLP290 in the 5xFAD mice improved spatial memory in the Morris Water Maze (MWM) test whereas it improved learning performance in the MWM and episodic memory in the Contextual Fear Conditioning test in the APPNL-G-F mice as compared to vehicle-treated controls. These results indicate that KCC2 may be a viable target for

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reversing deficits in GABAA-mediated inhibition in AD and attenuating several symptoms associated with AD pathology.

3-C-321: Driving the nuclear localization of endogenous alpha-synuclein to study Parkinson's disease in mice

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of alpha-synuclein (aSyn) throughout the brain. Although aSyn is natively found at the synapses and in the nucleus, previous studies from our lab and others have shown that its nuclear accumulation is proportional to its neurotoxicity and increases in the brain of PD patients. To further study nuclear aSyn, we created a novel mouse line (SncaNLS-Flag) in which endogenous flag-tagged aSyn is localized to the nucleus via a nuclear localization signal (NLS) tag. I have characterized this mouse line on a behavioural, histological, and biochemical level and tracked the progression of disease in young (2-3 months), mid-aged (8-9 months), and aged (18-19 months) mice. The SncaNLS-Flag/NLS-Flag mice show a significant motor deficit with age, as well as reduced fecal production and decreased survival rate. Histological and biochemical analyses of these mice show significant perturbations in the cortex, including cortical thinning and increased pyknotic cells. Additionally, there was no significant aggregation nor pS129 aSyn, suggesting these phenotypes are due to its nuclear accumulation and that the addition of the NLS-Flag tag does not significantly alter the aggregation kinetics of aSyn in vivo. This study stands to provide a new and useful pre-clinical model of PD. In addition, it will yield important insight into the mechanisms of aSyn-mediated toxicity, thereby identifying new avenues for therapeutic intervention in PD.

3-C-322: Trkb receptor activation alleviates early seizure-induced dysfunction of hippocampal fast-spiking interneurons

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Early life seizures (ELS) are often refractory to conventional anticonvulsant treatments, and can result in later life epilepsy and severe cognitive deficits. Our recent study demonstrated that ELS acutely reduced the excitatory synaptic inputs onto hippocampal fast-spiking (FS) interneurons through affecting presynaptic neurotransmitter release, which plays a crucial role in ELS pathophysiology. Thus, enhancing excitatory synaptic afferents onto FS interneurons will represent a logical approach to normalize the function of FS interneurons in ELS. BDNF regulates excitatory circuit development in FS interneurons through TrkB receptors. Therefore, we hypothesize that activation of TrkB receptors will alleviate ELS-induced dysfunction of excitatory afferents onto hippocampal FS interneurons. ELS were induced in P10-12 mice. We found that activation of TrkB receptors using a partial TrkB receptor agonist, LM22A-4, significantly increased the frequency of AMPA receptor mediated sEPSCs, but not sEPSC amplitude in CA1 FS interneurons in slices from 1 hour post-ELS mice, through increasing the probability of neurotransmitter release as evidenced by increased paired pulse ratio of evoked AMPAR EPSCs. Furthermore, LM22A-4's effects

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were abolished by co-administration of the TrkB receptor antagonist, ANA-12. These data strongly support a critical role of TrkB receptors in mediating ELS-induced dysregulation of hippocampal fast-spiking interneurons, and provide a potential therapeutic option for early life epilepsy.

3-C-323: It's in the timing: reduced temporal precision in neural activity of schizophrenia

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Studies of perception and cognition in schizophrenia (SCZ) show neuronal background noise (ongoing activity) to intermittently overwhelm external stimulus processing. This increased relative noise results in temporal imprecision and higher variability of behavioral responses. What, however, are the neural correlates of temporal imprecision in SCZ behavior? We report EEG decrease in signal-to-noise ratio (SNR) in two SCZ groups (but not in depression) in broadband, theta, and alpha bands. SCZ also show lower intertrial phase coherence (ITPC) relative to stimulus onset in theta which, as computational simulations show, is due to phase-based temporal desynchronization. Reduced SNR and ITPC are related and show a relationship to temporal precision on the behavioral level, namely reaction times. In conclusion, we demonstrate how diagnostic-specific temporal imprecision in SCZ neural activity - reduced relative signal strength and phase coherence - mediates temporal imprecision on the behavioral level. Temporal imprecision may underlie the altered neuro-cognitive processing in SCZ.

3-C-324: Dissecting the lateral hypothalamic input to the dorsal raphe nucleus and its role in major depression

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Disturbance of the central serotonin system has long been thought of playing a leading role in major depressive disorder. The main serotonergic nucleus of the brain, the dorsal raphe nucleus (DRN), integrates inputs from multiple brain regions, a large fraction of which is coming from the lateral hypothalamic area (LHA). In this study, we have examined whether plasticity at the LHA-DRN pathway contributes to the development of depressive or resilient phenotypes in mice undergoing chronic social stress. To activate LHA terminals in DRN, an AAV-ChR2-YFP was injected in the LHA of 6 weeks old C57BL/6J male mice. Two weeks later, these mice were subjected to chronic social defeat stress (CSDS) protocol. 24-h after CSDS, mice were classified as either susceptible or resilient when evaluated in a social interaction test, and acute brain slices encompassing the DRN were prepared. During whole-cell patch-clamp recordings of DRN neurons, 5 ms blue light pulses were delivered to activate LHA axons terminals, and postsynaptic currents were measured to investigate pre- and postsynaptic plasticity. In resilient mice, we found a significant increase in paired-pulse ratio at GABAergic synapses, indicating the decreased GABA release probability. In susceptible mice, we measured an important trend toward a decrease in the AMPAr/NMDAr ratio, indicating synaptic depression at the LHA-DRN pathway caused by CSDS. These results suggest that synaptic dysfunction may play an important role in the behavioral phenotype found in depression.

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3-C-325: Targeting post-stroke white matter microgliosis using minocycline to prevent cognitive decline in the rat

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Microglia activation is a critical component of the post-stroke inflammatory response; however, an accumulation of pro-inflammatory activated microglia can have a detrimental effect and lead to cognitive decline. Strokes that affect the basal ganglia can impair behavioural flexibility, an important component of executive function. An association between activated microglia in the white matter tracts and executive dysfunction has been established but not sufficiently evaluated in the context of stroke. Minocycline is a tetracycline derivative shown to effectively inhibit microglia activation. In this study, we used a rat model to investigate the effects of acute post-stroke minocycline treatment on cognitive outcomes and white matter pathology. Stroke was induced in 8-10-month-old male wildtype Fischer 344 rats by injection of endothelin-1 into the right dorsal striatum. Minocycline was administered for 4 days post-stroke prior to testing for behavioural flexibility, learning and memory using an operant conditioning-based set-shifting task and the Morris water maze. Brains were histologically examined at 28 days post-stroke to assess microglia activation, astrogliosis and infarct size. Results indicate a link between white matter activated microgliosis and behavioural outcomes post-stroke suggesting that modifying microglia activation post-stroke could protect the brain and improve cognitive outcomes.

3-C-326: A novel assessment of motor function sensitive to upper and lower motor neuron loss in ALS

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that results in catastrophic muscle weakness and degeneration. The clinical hallmarks of the disease include the presence of both upper and lower motor neuron (UMN/LMN) degeneration throughout the corticospinal tract (CST), specifically in the motor cortex, brainstem, and spinal cord. The focal point of degeneration in the CST largely determines the disease presentation, which include bulbar-onset, limb-onset, and pure UMN- or LMN-associated ALS. Some ALS subtypes tend to lead to better prognoses; thus, it is crucial to understand the specificities of the different presentations of ALS. In the preclinical setting, sensitive functional tests that can detect early changes in motor function associated with the disease progression in rodents are critical to understanding the etiology of the disease and treatment development. Using the SOD1*G93A mouse model, we have established a novel motor performance assessment that is sensitive to early loss of both UMNs and LMNs. We use a rope-pulling paradigm to assess forelimb and hindlimb function. Our findings indicate that early loss of LMNs in the L5-spinal cord is correlated with decreased hindlimb function, while the gradual loss of UMNs in the layer-5 of the motor cortex is primarily associated with decreased forelimb function. This test may be sensitive to motor deficits earlier than other conventional motor performance tests. These findings could provide novel insights into the pathogenesis of ALS and offer detailed evaluation of potential treatments.

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3-C-327: LRRK2 mediated microglial phenotype and neurotoxicity in a novel two-hit in vitro model of neurodegeneration

Shawn Hayley[1]

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Background: The in vitro characterization of transitional microglial states in the context of neurodegeneration is lacking; therefore, we report a novel classification system that tracks microglial activation state and potential neurotoxicity. Furthermore, we were interested in the role of leucine rich repeat kinase2 (LRRK2) in this regard, given its importance in inflammatory processes and that it is implicated in Parkinson's Disease (PD). Methods: Differentiated neuronal SH-SY5Y cells were pre-stressed with sub-toxic levels of glutamate prior to co-culture with lipopolysaccharide-activated microglial BV2 cells or primary microglia. Both transwell co-cultures and mixed live-cell imaging was used to asses microglial transition through various morphological phenotypes and their impact on SH-SY5Y cells. Results: Healthy neurons were resistant to microglial-mediated inflammation but pre-stressed neurons were highly susceptible. Pre-stressed neurons actively recruited microglia, which expressed high levels of oxidative stress and formed large cellular aggregates. LRRK2 kinase and WAVE2 inhibitors (MLi2 and CK-869, respectively) stunted microglial activation and reduced pro-inflammatory cytokines. Conclusion: LRRK2 and WAVE2 may be important mediators in microglial-induced neurotoxicity and these data may be mechanistically important for better understanding neuron-microglial crosstalk and its role in neurodegenerative conditions.

3-C-328: Characterizing gut dysbiosis and the gut derived immune response to ischemic stroke

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Ischemic stroke is a devastating neurological disease caused by a reduction in blood flow to the brain that results in neuronal cell death. Subsequent neuroinflammation is mediated by central nervous system resident immune cells and peripheral immune cells. Evidence suggests that stroke-induced gut dysbiosis results in priming of pro-inflammatory immune cells in the intestine that migrate to the stroke lesion and contribute to neuroinflammation. Currently, it is unknown whether gut dysbiosis and the migration of gut-derived immune cells to the stroke lesion persist in the chronic phase following injury. In this study, we aimed to characterize; (I) stroke induced gut dysbiosis and (II) the contribution of gut-derived immune cells to neuroinflammation, over time in a rodent model of ischemic stroke. Using 16s rRNA sequencing we observed that gut dysbiosis is observed at D4 following injury in both males and female animals. Interestingly, females exhibit a return to baseline microbial composition at D20 while males continue to exhibit gut dysbiosis. In addition, we injected a lipophilic cell-tracking dye (Cm-DiI) into peyer's patches at various timepoints following injury to observe whether gut derived immune cells migrate to the brain beyond D3. Using immunohistochemical analyses, we observed Cm-DiI+/CD45+/DAPI+ cells in the stroke injured hemisphere at D4 and D9 following ischemic stroke induction. These findings suggest that stroke induced gut dysbiosis and the migration of gut-derived immune cells to the stroke lesion are phenomena that persist beyond the acute phase of injury.

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3-C-329: Nuclear Laminopathy and oxidative stress in Alzheimer's Disease

Shakila Sultana[1], Tetiana Shcholok[1], Md Imamul Islam[1], Eftekhar Eftekharpour[1]

[1]University of Manitoba

Alzheimer's Disease (AD) remains the major form of Dementia. Progressive neuronal loss is the major cause for the disease; however, the etiology of AD remains a controversial topic. Excessive oxidative stress, Tau hyperphosphorylation and formation of intracellular neurofibrillary tangles, as well as accumulation of extracellular Amyloid beta plaques represent the main targets for finding a cure. There is currently no effective treatment available for AD. Loss of cellular antioxidants including Thioredixin-1 (Trx1) is observed in AD tissue samples. Trx1 is a small redox reductase protein responsible for maintaining the oxidized proteins. Examining the importance of Trx1 depletion in pathology of AD, we have previously shown that pharmacological and genetic inhibition of Trx1 impairs autophagy, a vital housekeeping process responsible for protein homeostasis in neurons. We also have identified that loss of Trx1 is an important upstream event in induction of neuronal nuclear lamina invagination. Nuclear lamina damage or laminopathy is a newly identified mechanism in pathophysiology of AD. In the current studies we use genetic inhibition of Trx1 in human neuroblastoma cells and examine the effect on nuclear events. Our results indicate that downregulation of Trx1 is sufficient for induction of NL damage. These results lead to histone modification and changes in nuclear chromatin methylation. These studies were also complemented in hippocampi tissues from a mouse model of neuronal specific Trx1 knockout. Downregulation of Trx1 in these mice was associated with nuclear lamina damage and accumulation of amyloid beta and Tau hyperphosphorylation. Our studies provide a mechanistic link between oxidative stress and the key downstream events observed in AD pathology.

3-C-330: Effect of 5α-androstane-3α,17β-diol on ERK and MKP3 in a mouse model of Alzheimer's Disease

Simran Bhullar[1], Nariko Kuwahara[1], Kate Nicholson[1], Lauren Isaacs[1], Boyer Winters[1], Neil MacLusky[1]

[1]University of Guelph

Alzheimer's Disease (AD) is more common in women, while low free testosterone has been associated with increased AD risk in men. However, treatment with testosterone has yielded mixed results in improving AD-related cognitive decline. Previous in vitro studies have shown that a major neurometabolite of testosterone: 5α-androstane-3α,17β-diol (3α-diol) inhibited the prolonged extracellular signal-regulated kinase (ERK) phosphorylation associated with oxidative stress. The role of 3α-diol in vivo remains unknown. We therefore examined the effects of continuous 3α-diol treatment on protein markers associated with AD progression in a triple transgenic (3xTg) mouse model. 3-month-old wild-type and 3xTg mice received subcutaneous implants of a 1 cm long Silastic capsule containing either 3α-diol dipropionate, or a blank capsule. Brains were collected at 6 and 9 months of age to analyze changes in expression of hippocampal ERK, MAP Kinase Phosphatase 3 (MKP3), plus phosphorylated (Ser202) and total tau. 3α-diol had no significant effect on the ratio of phosphorylated: total tau, at either age. No significant differences in ERK phosphorylation were observed at 6 months, but at 9 months sex and genotype-dependent differences were observed, with 9-month 3xTg females exhibiting higher ERK phosphorylation as well as markedly higher MKP3

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expression. Treatment with 3α-diol had no effect on ERK phosphorylation, but significantly reduced MKP3 at 9 months, to levels indistinguishable from those observed in 3xTg males. 3α-diol may contribute to sex differences in AD susceptibility.

3-C-331: Elucidating functional connectivity differences amongst older adults with mild cognitive impairment, subjective cognitive decline or normal cognition

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Reduced ability of the salience network (SN) to control switching between the central executive and default mode network (DMN) is linked to deterioration of cognitive functioning in normal aging, mild cognitive impairment (MCI) and AD dementia (He et al., 2014). In the current study, we compared functional connectivity between SN and the anterior DMN amongst older adults with subjective cognitive decline (SCD), MCI, and normal cognition (NC). Participants were 72 older adults [39 females, mean age=71.5] who were classified as either NC (n=26), SCD (n=29), or MCI (n=17). Participants underwent a 6-minute resting state functional magnetic resonance imaging using gradient-echo EPI BOLD at 3T (TR=2000ms, TE=30ms). Seed-based analysis using CONN with an anterior cingulate cortex (ACC; [0, 22,35]) seed, a key node in the SN, was conducted to assess functional connectivity between the SN and the anterior DMN within each group. Groups did not differ in age, years of education, or sex distribution [$F(2,69)=0.415$, $p=0.66$; $F(2,69)=2.20$, $p=0.12$; X^2 (2, $N=72)=1.89$, $p=0.39$, respectively]. Significant functional connectivity was found between ACC and medial prefrontal cortex (mPFC) in SCD and MCI groups ($T(28)=2.39$, p-FDR=0.04; $T(16)=2.89$, p-FDR=0.02, respectively) but not in the NC group. These findings show support for increased functional connectivity in SCD and MCI between SN and anterior DMN compared to NC. This finding is consistent with evidence of increased functional connectivity between the posterior DMN and mPFC in individuals with MCI and AD, an alteration that is believed to be a compensatory response to decreased functional connectivity between the posterior DMN and other brain regions such as the medial temporal lobe, responsible for memory formation and processing.

3-C-332: Cellular senescence and cognitive impairment following repeated mild traumatic brain injury in mice

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Mild traumatic brain injury (mTBI) is common and considered a Canadian public health issue. While some patients recover shortly after injury, others experience long-term symptoms including memory problems, executive dysfunction, behavioural changes, and mood disorders, along with increased risk of neurodegenerative disease. The precise mechanisms by which mTBI causes these changes remain unclear. We hypothesize that mTBI induces cellular senescence, leading to largescale signaling changes which contribute to neurological dysfunction. Here we have utilized an in vivo experimental model of mTBI in mice. Briefly, sex-balanced groups of adult C57BL/6 mice were anesthetized and exposed to three mTBIs with a 24h inter-injury interval via an electromagnetic driven piston or sham

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surgeries. Mice underwent behavioural testing for the light-dark task, elevated maze task, and Morris water maze task. These tests indicate that mTBI mice have impaired learning, memory, and executive functioning at 1 week and 6-weeks post-injury compared to shams, with sex-dependent changes in risk-taking behaviour and anxiety at 1 week. Molecular analyses (RT-PCR, Western Blot, histology) show evidence of DNA damage and upregulation of DNA damage induced cellular senescence pathways. Single-cell RNA sequencing of mTBI and sham brains at 1-week post-injury revealed largescale signaling changes consistent with cellular senescence and altered neuronal networks. This study has identified senescence as a mechanism by which mTBI leads to neurobehavioural and cognitive deficits and long-term brain dysfunction.

3-C-333: Understanding the therapeutic effects of transcranial direct current stimulation in parkinson's disease

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Parkinson's Disease (PD) is a debilitating disease of motor functioning, affecting approximately 3% of individuals over the age of 60. The clinical motor symptoms of PD don't appear until 70% degeneration of dopaminergic neurons (DA) in the substantia nigra (SN). Currently, there is no cure. And the treatment options available usually fail to prevent the underlying cause of degenerative changes. Interestingly, clinical reports have shown marked improvements in the motor symptoms of PD patients following the onset of seizures. However, the mechanism behind this improvement is completely unknown. Transcranial direct current stimulation (tDCS) is an extremely safe, clinically relevant tool to rapidly increase neuronal excitability and firing activity. Here, we aim to determine how tDCS affects PD pathology through increasing neuronal activity in the basal ganglia pathway. Using an in vitro model of PD we demonstrate that elevating neuronal membrane potential through tDCS significantly reduces the intracellular accumulation of α-synuclein fibrils. In vivo, we have shown that tDCS effectively activates basal ganglia structures that show decreased activity in PD mouse models. These results strongly support that tDCS may have disease modifying effects on the progression of PD through alleviating the attenuation of basal ganglia activity and promoting the clearance of toxic α-synuclein fibrils. Taken together, these results contribute to a better understanding of neuronal activity in PD onset and progression and suggest tDCS as a novel strategy for early intervention in PD.

3-C-334: Identification of the interleukin-1 beta maturation mechanisms in the EAE mouse model of multiple sclerosis

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BACKGROUND: Multiple sclerosis (MS) is an autoimmune disease characterized by inflammation of the central nervous system and loss of neurological functions. The molecular mechanisms underlying this abnormal reaction, however, remain unknown. We recently highlighted the importance of interleukin (IL)-1β in MS with a mouse model mimicking the disease: experimental autoimmune encephalomyelitis (EAE). Notably, we showed that mice lacking IL-1β are protected against the development of EAE. Thus, we hypothesized that inactivation of the inflammasome, a multiprotein complex stimulating the maturation of IL-1β

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using the adaptor protein ASC, would prevent the development of EAE disease. METHODS: EAE disease was induced in mice lacking ASC (ASC-KO) and the molecular mechanisms leading to the cleavage of IL-1β were characterized in an in vitro model of blood-brain barrier (BBB) transmigration. RESULTS: We observed that the absence of ASC does not protect mice against EAE, suggesting that the mature form of IL-1β is still produced despite inflammasome inhibition. We further found that in ASC-KO mice characterized by the absence of inflammasome activity, monocytes are the main source of mature IL-1β during EAE. Finally, we discovered that ASC-KO monocytes can produce the mature form of IL-1β when migrated across BBB-endothelial cells. CONCLUSION: Considering the crucial role that IL-1β plays in EAE and possibly MS, a better understanding of the mechanisms responsible for the alternative, inflammasome-independent, cleavage of IL-1β could help prevent neuroinflammation and CNS autoimmunity.

3-C-335: Neuroinflammation facilitates chemotherapy induced neuropathic pain

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Chemotherapy-induced neuropathic pain (CINP) is a treatment-limiting complication of several classes of anticancer agents, including the taxanes, platins, vinca alkaloids, and bortezomib. It negatively affects the quality of life of patients, and unfortunately, there is no effective treatment at present. The current treatment approaches utilize antidepressant drugs, which offer only mild improvement. Despite several research efforts in the past, the underlying mechanism behind CINP is not clear, which poses a major hurdle in developing effective therapies. In this study, we explored if neuroinflammation has any role in inducing CINP. We considered the frequently used chemotherapy agents paclitaxel and cisplatin in this study. Intraperitoneal administration of either paclitaxel or cisplatin demonstrated robust mechanical allodynia in male CD-1 mice. Co-administration of an anti-inflammatory agent, dexamethasone, significantly reversed mechanical allodynia in these models. We further investigated the impact of these drugs on neurite outgrowth of DRG cultures established from paclitaxel/cisplatin treated animals and did not observe any significant effect. However, these drugs induced hind paw denervation in these animals, and dexamethasone reversed the loss of the nerve extremities in the paws, as evident from increased PGP9.5 labeling of nerve fibers. Evaluation of macrophages' response to these drug treatments in the DRGs and nerve extremities is ongoing. Overall, our findings suggest that local inflammatory response at the nerve extremities contributes to CINP.

3-C-336: Insulin for retinal ganglion cell dendrite regeneration: effect of intraocular pressure and identification of multiple downstream pathways

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Purpose: The retraction of retinal ganglion cell (RGC) dendrites is one of the earliest pathological changes leading to functional deficits. We demonstrated that insulin, administered after arbor retraction, promotes RGC dendrite and synapse regeneration. Endogenous insulin and related molecules are naturally found in the retina. Thus, we asked the following questions: 1) is reduction of high intraocular pressure (IOP) sufficient to promote dendrite regeneration in the absence of exogenous insulin? 2) what are the

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signaling components downstream of insulin that stimulate RGC dendrite regeneration in glaucoma? Methods: Thy1-YFP mice, which allow visualization of RGC dendritic arbors, received an intracameral injection of magnetic microbeads to induce ocular hypertension. Daily topical application of brinzolamide, a carbonic anhydrase inhibitor with negligible effects on neurons or vascular cells, was used to reduce IOP. RGC dendrites were imaged with confocal microscopy and 3D reconstructed using Imaris software. RGCs were isolated by Fluorescence Activated Cell Sorting (FACS) from insulin- or vehicle-treated glaucomatous retinas as well as sham-operated controls, followed by RNA sequencing analysis (RNA-seq). Results: Brinzolamide effectively reduced IOP relative to vehicle-treated controls (sham: 10.7±0.3 mmHg, brinzolamide: 11.3±0.4 mmHg, vehicle: 20.5±0.8 mmHg, n=12 mice/group, Student's t-test, $p<0.001$). Total RGC dendritic length and complexity increased in glaucomatous eyes treated with insulin (4,515±149 µm) to values similar to those found in non-injured controls (4,566±233 µm), but not in eyes treated with brinzolamide (2,534±164 µm) or vehicle (2,981±169 µm) (n=6 mice/group, ANOVA, $p<0.001$). RNA-seq analysis of insulin- and vehicle-treated glaucomatous re

3-C-337: The neurosteroid 5α-androstane-3α,17β-diol exerts neuroprotective effects in the 3xTg mouse model of Alzheimer's disease

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Age-related decreases in gonadal steroid hormone levels have been associated with cognitive decline and an increased risk of developing Alzheimer's disease (AD). The incidence of AD is higher in women than men, and women experience worsened cognitive deterioration at the same stage of the disease. This may in part, reflect the neuroprotective effects of testosterone, since men with high free testosterone levels maintained into old age have a reduced risk of developing AD. Recent in vitro studies have demonstrated that 5a-reduced neurosteroid metabolites of testosterone, including 5α-androstane-3α,17β-diol (3α-diol), may contribute to these neuroprotective effects conferred by the parent hormone and may contribute to the observed sex differences in disease incidence and severity. However, the possible protective effects of 3α-diol itself in vivo remains unknown. To determine whether supplementation with 3α-diol might confer protection against the development of AD-like pathology, male and female 3xTg-AD mice were implanted s.c. with Silastic capsules releasing 3α-diol at 3 months of age. After 6 months of treatment, 3α-diol increased hippocampal dendritic branching in females compared to males, and improved object recognition memory (ORM) in 3xTg-AD females, eliminating the sex difference normally observed at this age. Therefore, 3α-diol appears to exert sex-specific neuroprotective effects in this mouse model of AD. Ongoing experiments are exploring the effects of 3α-diol on cognitive performance and dendritic morphology in older 3xTg mice, once AD-related pathology has further progressed.

3-C-338: Lateralized neuroinflammatory response in white matter and subcortical autonomic nuclei following selective insular ischemic stroke provides links to cardiac injury

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Ischemic stroke (IS) patients with damage to the insula, a region that controls cardiac autonomic regulation, encounter worsened stroke-induced heart injury (SIHI). Despite the association between IS and incident heart disease, the pathophysiology of SIHI remains unknown. We hypothesize that central autonomic network (CAN) nuclei, which convey autonomic information from insula to heart, and connecting white matter tracts, are potential mediators of SIHI. Here, we aim to characterize the neuroinflammatory profile of these regions following lateralized endothelin-1 (ET-1)-induced insular IS. IS was induced in left or right insula of 6-mo male Wistar rats via ET-1 stereotaxic injection. Control rats received saline injection. Cortical and subcortical CAN nuclei as well as bidirectional white matter tracts were examined 28 d post-IS for OX6+ MHCII microglia and GFAP+ astrocytes. Masson's trichrome staining assessed cardiac fibrosis. We found lateralized effects in white matter microgliosis and astrogliosis in specific CAN nuclei, such as the sympathetic locus coeruleus and parasympathetic nucleus of the solitary tract medial. White matter microgliosis was positively correlated with left atrial fibrosis. For the first time, we provide an in-depth neuroinflammatory analysis following lateralized insular IS. The interplay between white matter microgliosis and astrogliosis in subcortical CAN nuclei implicate neuroinflammation in the pathogenesis of SIHI, serving as a therapeutic target. Future work should determine cardiac autonomic consequences and role of astrocytes in CAN nuclei.

3-C-339: Multi-scale analysis of astrocyte morphology and ultrastructure in healthy and Alzheimer's disease model mice

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Astrocytes comprise a highly complex cell population with diverse structural and functional properties in both the healthy and diseased central nervous system. Astrocytic pathology has been implicated in numerous neurodegenerative diseases, however, their structural rearrangement in brain diseases such as Alzheimer's disease (AD) remain poorly understood. Here, we applied super-resolution imaging and 3-dimensional (3D) electron microscopy approaches to better understand the structural changes of astrocytes in AD model (APP/PS1) mice. Structured illumination microscopy (SIM) of genetically-labeled astrocytes allowed us to capture global modifications to individual astrocyte shape while resolving certain aspects of their subcellular organelle distribution. We observed perturbations to the complex branching pattern of whole astrocytes and additionally, mapped the organization of mitochondria throughout the cell in AD model samples. Results from SIM imaging were complemented with analysis using focused ion beam scanning electron microscopy (FIB-SEM) that enabled 3D serial reconstruction of astrocyte ultrastructure. Using FIB-SEM, we found dramatic restructuring of astrocyte subcompartments in neuropil and astrocytic endfeet, including major alterations of astrocytic process shape and the restructuring/redistribution of mitochondria. Quantitative analysis of SIM and FIB-SEM approaches allowed us to directly compare the astrocytic surface structure and the organelle distribution/morphology within astrocyte sub-compartments using custom MATLAB scripts, in healthy and AD model tissue. This multi-level structural analysis of astrocytes provides an

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important understanding of how astrocytes are constructed in the healthy brain and altered with brain disease.

3-C-340: Characterizing cellular defects of adult hippocampal neurogenesis in a mouse model of Alzheimer's disease

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Alzheimer's disease (AD), marked by a serious and progressive decline in cognitive abilities, is a severely debilitating disease that is becoming an increasing concern with our aging population. Defects in neurogenesis have been shown to exist in AD and aggravate the neuropathology and cognitive deficits associated with the disease. Study of the underlying mechanisms behind these defects can reveal promising and novel therapeutic avenues. To identify these defects, we performed a preliminary immunohistochemistry characterization using the triple transgenic mouse model of AD (3xTG), where the expression of early stage (Sox2), later stage (Dcx) and proliferative (EdU) markers were analyzed in neural stem and progenitor cells (NSPCs) in the hippocampus of control and 3xTG mice. This analysis revealed deficiencies in Sox2, Dcx and EdU positive cells in 3xTG mice, suggesting a loss of NSPCs along the neurogenic process. To identify in which populations this loss was occurring, we conducted a single cell RNA sequencing experiment on NSPCs sorted from the hippocampus of control and 3xTG mice from our Nestin-Cre YFP reporter lines. This allowed us to map distinct cell populations as the NSPCs progressed through neurogenesis and our preliminary analyses demonstrate that there are defects in specific 3xTG NSPCs populations, impairing their progression through neurogenesis. Further characterization of these cellular defects and underlying molecular mechanisms can reveal novel therapeutic strategies for AD. This work is funded by CIHR and there are no conflicts of interest to report.

3-C-341: Elucidating the endogenous distribution, topography and cells-of-origin of a-synuclein in relation to Parkinson's disease

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Parkinson's Disease (PD) pathologically presents with the inclusion of Lewy bodies in the brain, as well as dopaminergic degeneration, two features that are thought to be intrinsically tied to PD symptomology. Lewy bodies are composed of aggregated α-synuclein protein, and despite their initial description over 100 years ago, little is known about their pathological and native properties. Nevertheless, α-synuclein clearly merits additional investigation since not only is it highly abundant in Lewy bodies, but its overexpression in humans and animal models causes PD like phenotypes. Due to its cytoplasmic localization, immunostaining results in unclear staining patterns, limiting our insight into the cell types α-synuclein naturally occupies and what circuits may be impacted by its accumulation. Using a mouse model that localizes α-synuclein to the nucleus of cells (SncaNLS-Flag) to overcome visualization issues, we can map out the topography and cells-of-origin of α-synuclein in the brain and periphery of mice. To do so, we performed immunohistochemistry on SncaNLS-Flag mouse brain and periphery tissue. Using ilastik to conduct machine learning analysis on results from staining, we determined regions with high α-synuclein expression, which were

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subsequently co-stained with cell-type specific markers. Granule, pyramidal, mitral, dopaminergic and layer-specific cortical neurons appear to show co-localization with α-synuclein and are therefore likely to be the cellular origins of the protein. α-synuclein shows a clear cell-type specific expression profile, giving insight into what cellular populations are most vulnerable to PD pathology. Further studies will focus on observing how α-synuclein changes in response to treatment with PD-linked insults.

3-C-342: In vivo striatal neural activity during motor skill learning and spontaneous behaviour in Huntington's Disease mice

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Huntington's disease (HD) is a neurodegenerative disorder characterized by motor, cognitive and psychiatric deficits. The dorsal striatum is the major site of neurodegeneration in HD, particularly the D2-expressing spiny projection neurons (D2-SPNs) early on, and the D1-expressing SPNs (D1-SPNs) late in the disease. Studies have shown aberrant cortico-striatal signalling in HD mice, including deficits in cortico-striatal plasticity. Although there has been extensive research on changes to cortico-striatal signalling in vitro, there has been relatively little research on how these changes correlate with behaviour in vivo. We combined the accelerating rotarod and open field tasks with GCaMP7f imaging using fiber photometry to correlate activity of striatal neurons with task performance and motor learning. Both WT and YAC128 HD mice showed increased striatal activity over baseline when they performed the rotarod, and this activity reduced over days of training. However, we found significant disruptions in the correlation between striatal activity and behaviour on the rotarod and in the open field in YAC128 HD mice. We also discovered changes to paw kinematics during rotarod in YAC128 mice, even when mice had no differences in latency to fall. We are also performing experiments measuring activity of D1-SPNs and D2-SPNs simultaneously, in YAC128 and Q175 HD mice. This work begins to bridge the gap between our understanding of cortico-striatal changes determined from in vitro studies and the behavioural deficits observed in vivo.

3-C-343: Glutamate uptake asymmetry in a mouse model of alzheimer disease

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Sodium-dependent high affinity glutamate transporters are essential in mitigating the toxic effects of extracellular glutamate accumulation. Glutamate uptake is primarily mediated by astrocytes, although glial coverage is reported to be four times higher postsynaptically than presynaptically. The functional consequences of this synapse asymmetry in glial coverage is poorly understood, but it implies the presynapse is more vulnerable to glutamate uptake impairments than the postsynapse in brain diseases with compromised glutamate uptake, such as Alzheimer disease (AD). Here, we developed a novel approach to quantify the unique glutamate clearance dynamics in presynaptic and postsynaptic microenvironments in the hippocampus of the 3xTg mouse model of AD through a combination of intensity-based glutamate sensing fluorescent reporter (iGluSnFR) and two-photon microscopy. By 6-months, an age corresponding to the emergence of an AD-like phenotype in the 3xTg mouse, glutamate clearance in presynaptic microenviornments was impaired while clearance

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in postsynaptic microenvironments was unimpaired in 3xTg mice. This impairment is mediated by GLT-1 as confirmed by 2 observations: DHK application to acute hippocampal slices increases glutamate clearance time in presynaptic microenvironments, but the extent of this increase is lesser in 3xTg mice compared to control mice; and EAAT2 overexpression via ceftriaxone speeds up glutamate clearance in presynaptic microenvironments. This implies that glutamate transporters have different capabilities depending on the specific microenvironment within a given region, and in the context of AD, suggests that the emergence of presynaptic microenvironment glutamate clearance deficits may correlate with the emergence of AD-like synaptic pathology

3-C-344: Purkinje cell intrinsic firing deficits precede cell death and motor impairment in a mouse model of Christianson syndrome

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One of the most vulnerable neuronal cell types in the mammalian brain are cerebellar Purkinje cells (PC). In many ataxias, certain PCs show remarkable resilience to disease, with only a subpopulation of PCs typically vulnerable to the same insult. Recently we have found that certain PCs located in the anterior region of the cerebellar vermis are more likely to die than those located in the posterior region in Christianson syndrome (CS) ataxia. We now wish to investigate what leads to PC vulnerabilities versus resilience in CS ataxia. CS 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 recycling endosomes of the endocytic pathway. Loss of NHE6 results in over acidification of endosomes leading to mistrafficking of cargo which could affect neuronal function. PCs have a unique ability to fire high frequency action potentials, even in the absence of synaptic input and motor control. Using electrophysiology techniques we investigated if PCs in the anterior region have alterations in intrinsic firing prior to cell death and motor deficits in CS. Using a mouse model of CS (NHE6KO), we observed a significant decrease in PC intrinsic firing ability in the anterior region at age P40, an age which precedes manifestation of PC death and motor impairment. Given these results, we are testing therapeutic approaches targeting intrinsic firing in vulnerable PCs with the goal of restoring firing output and prevent behavioral deficits.

3-C-345: Mapping and characterizing ALS-linked TDP-43 protein-protein interactions

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Amyotrophic lateral sclerosis (ALS) is a moto-neuron disorder in which an RNA-binding protein, TDP-43, mislocalizes and pathologically accumulates from its normal nuclear locale to the cytosol. Given that the subcellular localization and expression of TDP-43 is tightly regulated and affected by its protein-protein interactions (PPIs), we posit that identifying novel interactors of wild-type and mutant TDP-43 could reveal insight into networks involved in driving ALS pathogenesis. Using CRISPR/Cas9, our lab has generated knockin cell lines expressing GFP-tagged wildtype (WT) and an ALS-causing mutant (Q331K) TDP-43, in the endogenous TARDBP locus (coding for TDP-43). We have shown that the Q331K mutation

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causes loss-of-function and mislocalization of TDP-43. We have performed immunoprecipitation-mass spectrometry (IP-MS) on these cell lines to elucidate interactors of WT- and Q331K, TDP-43. Our data has shown that there is an overall loss of interactors with the Q331K mutation. We have analyzed these data using bioinformatic approaches to shortlist and validate 14 candidates. From this, 4 interactors have shown robust interaction with TDP-43 via IP-western blot. We are using cellular and biochemical assays to assess the effects of knockdown and overexpression of these top 4 hits on TDP-43 localization and loss-of-function. Using this unbiased approach, we will identify TDP-43 PPIs and characterize their roles in cellular functions in the context of ALS, giving insight into pathways involved in driving neurodegeneration.

3-C-346: Investigating neurodevelopmental and axonal defects in human models of the 15q13.3 microdeletion disorder

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The 15q13.3 microdeletion syndrome is a highly penetrant copy number variant (CNV) associated with epilepsy, autism spectrum disorder, schizophrenia, and intellectual disability. Within the deletion are seven protein coding genes, including the deubiquitinase and driver gene, OTUD7A. We used a proximity proteomics assay in neurons to determine the binding partners to OTUD7A and found enrichment in proteins localized to the axon and axon initial segment (AIS). Using neurons generated from our cohort of 15q13.3 patient-derived induced pluripotent stem cells (iPSCs), we sought to understand the role of OTUD7A at the axon in 2D and 3D models of the CNV. 15q13.3 and mutant OTUD7A patient-derived neurons were generated from iPSCs and assayed for early growth and axonal properties using immunofluorescence techniques. We found that OTUD7A interacts with the axon growth protein, Ankyrin B, and AIS regulator, Ankyrin G. We examined 15q13.3 neurons at an early timepoint during axon outgrowth and found an immature phenotype among three 15q13.3 probands. We then looked at a mature timepoint to find aberrant localization of Ankyrin G at the AIS. To better profile the developmental trajectory of the 15q13.3 CNV, we are examining cerebral organoids at various timepoints to investigate neural progenitor proliferation, cellular migration, and maturation in a 3D system across development.

3-C-347: Increased light scattering in multiple sclerosis measured by near-infrared spectroscopy may indicate mitochondrial swelling

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Background: We used frequency-domain near infrared spectroscopy (fdNIRS) to show that about 40% of MS patients have brain hypoxia - based on reduced cortical microvasculature hemoglobin saturation (StO2). Light scattering (μs) has not been previously studied in MS and may provide important information on brain edema and mitochondrial swelling in MS. Objective: We aimed to use fdNIRS to determine whether changes in light scattering occur in MS patients. Methods: StO2 and μs was measured (53 controls and 78 MS) at baseline. MS patients (39) were measured ≥12 months later. Data were compared at baseline using a t-test, and a paired samples t-test was used to compare between baseline and 1-year follow-

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up. Results: Patients had reduced StO2 and increased μs at baseline compared to controls (57.5±7.8, 61.4±6.2, p=0.003)(9.2±1.36, 8.7±1.34, p=0.015) respectively. There was no significant different in StO2 and μs at follow-up compared to baseline (56.3±6.6, 57.4±7.0, p=0.349)(9.4±1.5, 9.23±1.3, p=0.511) respectively. Conclusions: Increased μs and reduced StO2 occurs in MS patients. Prior studies have found that increased μs is characteristic of hypoxia-induced cerebral edema and has also occurred with mitochondrial swelling. The μs shows changes that may be a marker of either condition. This novel technology can provide non-invasive information about brain physiology and may be detecting mitochondrial damage in MS. fdNIRS may be a useful tool to detect pathologies such as cerebral edema and mitochondrial swelling in disorders of the nervous system.

3-C-348: Lysosomal transport dynamics in GBA-inhibited iPSC-derived human neurons

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Lysosomes are acidic organelles that contain a myriad of hydrolytic enzymes. In neurons, lysosomes traffic throughout the axons and dendrites to deliver catabolic enzymes to distal regions of the cell and maintain local degradative demands. Of the various lysosomal enzymes, glucocerebrosidase (GBA) is of particular interest due to its relationship with synucleinopathies such as Parkinson's Disease and Dementia with Lewy Bodies. Mutations in GBA are the most common genetic risk factor for synucleinopathies, but the mechanistic relationship is unclear. GBA cleaves the glycolipid glucosylceramide (GC) into glucose and ceramide, but mutations in GBA, or its catalytic inhibition, can disrupt the composition of the lysosomal membrane. The lysosomal membrane serves as the platform to which trafficking complexes are recruited and activated. Thus, we investigated if the prolonged catalytic inhibition of GBA by Conduritol B Epoxide (CBE) could interfere with lysosomal trafficking dynamics in axons. In human iPSC-derived cortical neurons treated with CBE for 10 days, we did not observe a change in the motile fraction, velocity, or run length of LAMP1-GFP vesicles. Additionally, we did not find any alterations in lysosomal size or density in the axon, dendrites, or neuronal cell bodies, despite complete inhibition of enzymatic activity. These results suggest that CBE-mediated inhibition of GBA in neurons does not directly impact lysosomal dynamics or size in the time course of our experiments.

3-C-349: Meningeal dendritic cells interactions with astrocytes elevate the kynurenine metabolic pathway to sustain neuropathic pain

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The previous study from our group has identified that after peripheral nerve injury there is an increase of kynurenine in the plasma, which seems to be involved in the maintenance of neuropathic pain. However, the mechanisms which peripheral kynurenine (Kyn) mediates neuropathic pain is unknown. Therefore, the aim of the present study was to test the hypothesis that peripheral Kyn reaches the spinal cord and maintain neuropathic pain by KMO metabolism, leading to downstream nociceptive metabolites. Methods: Spared Nerve

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Injury (SNI) model of neuropathic pain was induced in C57BL/6 mice and the following test and methods were used: von Frey filaments nociceptive test, Real-time PCR and western blotting, inhibition of KMO activity. This study was approved by the Local Ethical Commission in Animal Research (045/2013). Results: SNI induced mechanical allodynia in a time-dependent manner, which peaked from 7 up to 21 days. SNI- induced mechanical allodynia was associated with an increase in the expression of KMO in the spinal cord, mainly at day 10 and 14 after injury. KMO expression was restricted to spinal cord astrocytes. Functionally, pharmacological inhibitor against KMO injected intrathecally after SNI, reduced mechanical allodynia. Also, kyn injected systemically (i.v) promoted mechanical allodynia, which was educed when KMO was pharmacologically inhibited. In summary, these results indicated that after peripheral nerve injury spinal astrocytes-expressing KMO plays a critical role in the development of neuropathic pain. In conclusion, the kynurenine metabolic pathway is a critical link in the neuroimmune response after peripheral nerve injury in the maintenance of neuropathy.

3-C-350: Enhancement of CHRNA5 mRNA expression by upstream polymorphisms associated with preserved cognition and lessened neuropathology in an aged human population

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Single nucleotide polymorphisms (SNPs) in cholinergic system genes have been previously linked to Alzheimer's disease (AD). However, the genetic and cellular mechanisms of these associations remain unexplored. The identification of SNP effects at the level of gene expression and AD-related neuropathologies in human brain could provide evidence for the stratification of AD subjects into molecular subtypes and inform novel treatment strategies. We analyzed ante-mortem cognition and post-mortem neuropathology data from 1,050 elderly human subjects from the Religious Orders Study and Memory and Aging Project cohorts. All subjects had matched genotypic and post-mortem RNA sequencing data from prefrontal cortex (PFC), and 24 had PFC single-nucleus data available. Using general linear models, we replicated a previously-described positive effect of a six-SNP haplotype in an upstream region of CHRNA5 on levels of CHRNA5 mRNA in PFC bulk-tissue and single-nucleus data. CHRNA5 codes for the α5 subunit of the nicotinic receptor, which has been previously linked to nicotine dependence and attention deficits, but not AD. Upon further investigation, we identified a novel, sex-dependent association of this regulatory CHNRA5 haplotype with preserved cognitive status at death as well as lower levels of beta-amyloid and phosphorylated tau in brain. Together, our findings suggest a neuroprotective role for elevated CHRNA5 expression in brain, and ongoing work is investigating closely-associated cellular and molecular pathways.

3-C-351: Fibre-specific white matter structural reductions differentiate acoustic neuroma patients with one-sided hearing loss from individuals with normal hearing

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Acoustic neuroma (AN) tumours are a chief cause of one-sided hearing loss in adults. One-sided hearing loss results from auditory nerve compression by the tumour at the pontine level of the brainstem. Treating one-sided hearing loss will require identifying precision targets of white matter nerve fibre abnormalities at levels above the tumour site. However, white matter structure is small and complex, making it difficult to examine with traditional magnetic resonance imaging (MRI) techniques. Here, we used a state-of-the-art technique called a "fixel-based analysis" to identify fibre-specific, or "fixel"-level differences in white matter structure between AN patients with one-sided hearing loss and individuals with normal hearing. We hypothesized wide-spread reductions in white matter structure in the AN group, corresponding to the effects of brainstem compression and shifting, as well as asymmetric auditory deprivation. Diffusion-weighted MRI data was collected from left- (n = 58) and right-sided (n = 55) AN patients treated at the Toronto Western Hospital, and normal hearing healthy controls (n = 55) either tested at Toronto Western or obtained from the Cambridge Centre for Ageing and Neuroscience study. The fixel-based analysis model was used to identify microstructural differences in nerve fibre density, and macrostructural differences in fibre cross-section between groups. We found significant white matter micro- and macrostructural loss in the AN group across tracts extending from the brainstem to the cortex, including at the acoustic radiation. Our findings suggest white matter abnormalities across the whole-brain in AN patients with one-sided hearing loss, which may comprise a target list of regions important for auditory therapies and neuroprosthetic design.

3-C-352: Activating transcription factor 4 inhibits mTOR signalling to trigger PUMA-dependent neuronal apoptosis in models of parkinson's disease

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Parkinson's Disease (PD) is a is highlighted by the progressive loss of dopaminergic neurons in the substantia nigra. Mechanisms underlying this neuronal loss remain largely unknown. Previously we have demonstrated that ATF4, a key mediator of the Integrated Stress Response (ISR), is upregulated in dopaminergic neurons following exposure to MPP+, 6-OHDA, or humanized alpha-synuclein pre-formed fibrils (PFFs). Specifically, we determined that ATF4 induction promotes neuronal death through transcriptional activation of known death genes including pro-apoptotic BH3-only protein PUMA. Interestingly, despite ATF4 being required for PUMA activation, chromatin immunoprecipitation experiments have revealed that ATF4 does not interact directly with the PUMA promoter. Given this, in the current study we aim to characterize the indirect mechanism by which ATF4 activation signals PUMA-dependent neuron loss. Using mouse primary neurons, we demonstrate that ectopic ATF4 expression results in activation of Trib3, SESN2, and DDIT4, which have previously been implicated to have inhibitory activity on mTOR. Indeed, ectopic expression of ATF4 in neurons also results in downregulation of mTOR signaling and increases in neuronal apoptosis. Importantly, our current investigations, show that ATF4-deficient neurons are resistant to mTOR inhibition induced by exposure to a-syn PFFs or PD toxins. In addition, we show that pharmacological inhibition of mTOR results in significant increases in PUMA activation and promotes PUMA-dependent dopaminergic neuron loss. Ultimately, these results provide a novel signalling mechanism by which ATF4 indirectly activates PUMA through suppression of mTOR signalling and provides further evidence for targeting the ISR for the development of therapeutics for PD.

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3-C-353: Reproductive experience and APOEe4 genotype differentially influence neuroplasticity in middle-age

Bonnie Lee[1], Paula Duarte-Guterman[2], Stephanie Lieblich[3], Muna Ibrahim[3], Rand Eid[4], Yanhua Wen[3], Mel Cevizci[3], Yvonne Lamers[3], Liisa AM Galea[3]

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Females have a greater lifetime risk of Alzheimer's disease (AD) compared to males, differences which are further exacerbated with possession of APOEe4 alleles, the greatest genetic risk factor for sporadic AD. Although studying sex and gender differences are important, so is studying sex-linked factors such as parity (pregnancy and motherhood). Previous parity influences brain aging trajectories in both humans and rodents and may be associated with a greater risk of AD and greater neuropathology. Neuroinflammation is increased with AD, reduces hippocampal neurogenesis, and activates the tryptophan-kynurenine pathway (TKP), and all these factors are influenced by aging and parity. We investigated whether previous parity influences hippocampal neurogenesis, inflammation and the TKP in middle-aged rats, dependent on APOEe4 genotype. Age-matched wildtype (WT) and humanized (h) APOEe4 female rats were nulliparous (never mothered) or primiparous (first-time mothers). Middle-age (13-14 months old) rats were euthanized to examine neurogenesis, microglia and TKP metabolites. hAPOEe4 rats had higher levels of TKP metabolites than WT rats, and primiparous hAPOEe4 rats had a faster tryptophan metabolism rate than controls. hAPOEe4 rats have fewer microglia and more neural stem cells (Sox2) in the ventral, but not dorsal, hippocampus compared to controls. Primiparous rats had more neurogenesis in the dorsal, but not ventral, hippocampus, regardless of genotype. These findings indicate that past reproductive experience needs to be considered in aging research.

3-C-354: The role of glutamate co-transmission by serotonin neurons of the dorsal raphe nucleus in the expression of L-Dopa-induced dyskinesia

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Parkinson's disease is characterized by the progressive loss of midbrain dopaminergic neurons that innervate the striatum. The dopamine precursor (L-Dopa) is the most effective pharmacotherapy but its chronic use is hampered by adverse effects such as abnormal involuntary movements (AIMs), also termed L-Dopa-induced dyskinesia (LID). Recent studies have shown the crucial role of serotonin (5-HT) neurons in 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 many diverse behaviors and LID expression. We used CRIPSR-Cas9 technology and viral injections to knock-out or overexpress the vesicular glutamate transporter 3 (VGluT3), specifically in 5-HT neurons of the DRN in adult mice. After extensive behavioral testing, these mice were injected with 6-OHDA in the medial forebrain bundle to selectively lesion DA axons, and then treated with L-Dopa to induce AIMs. RNAscope and immunohistochemistry confirm the depletion or overexpression of VGluT3 in AAV-infected 5-HT neurons of the DRN. VGluT3-depleted mice show a loss of motor coordination but an increase of spontaneous activity, a higher impulsivity level and a slight increase in sociability and anxiety. While mice overexpressing

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VGluT3 exhibit solely a slight decrease of the motivation. After dopamine lesion and L-Dopa administration, VGluT3-depleted mice present exacerbated AIMs caused by L-Dopa administration at low dose, while mice overexpressing VGluT3 manifest worsen orolingual AIMs at higher dose. Glutamate that is co-released by 5-HT neurons of the DRN appears to be involved in the regulation of motor behaviors, impulsivity, anxiety, and sociability, as well as in the expression of LID.

3-C-355: Phenotypic profiling of microglia across remyelination and ageing

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Multiple sclerosis (MS) is a neurodegenerative disease which is largely associated with progressive disability. It is characterized by multiple focal demyelinating lesions where the extent of myelin loss correlates with the advancement of disease and also age. Substantial work has focused on preventing demyelination from occurring, but the alleviation of MS symptoms through regeneration of myelin, or remyelination, remains an under-researched area. Remyelination is associated with less clinical disability and linearly declines with age. This process is dependent upon microglia, the resident immune mediators of the central nervous system (CNS). Microglia are a heterogeneous phenotype, forming subpopulations that vary across development, anatomical regions and disease. Using advanced analytical tools and bioinformatic techniques, we show that a subpopulation of microglia arises at the onset of remyelination in a mouse model of MS which presents acute demyelination followed by spontaneous, but robust, remyelination. These remyelination-associated microglia (RAM) change their transcriptional signature throughout remyelination, moving from an Igf1/Irf7 dominated phenotype to one that is characterized by genes responsible for regeneration, such as Meg3. We have validated this by showing the expression of Igf1 and Irf7 within mouse lesions using RNA scope. We are currently sequencing microglia from aged, lesioned environments to assess how microglia responses differ through ageing

3-C-356: Vulnerability to tau pathology in the entorhinal-hippocampal circuit

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The lateral entorhinal cortex (LEC) is the site of tau accumulation in early stages of Alzheimer's disease and has projections downstream to the dentate gyrus (DG) of the hippocampus. The pathological form of tau has the ability to propagate across synapses, spreading to connected brain regions and correlating with memory deficits and synaptic loss. The DG is the site of ongoing adult neurogenesis, with new granule neurons added showing enhanced plasticity and increased survival compared to older neurons. Thus, we are interested in examining neuron age for vulnerability to tau pathology in the LEC-DG circuit. We use an inducible cre-recombinase transgenic mouse model to label neurons born at different ages (development vs. adulthood) with TdTomato, and viral AAV tau injections into the LEC to mimic early tau pathology. Following a 4-month incubation, animals are tested for memory deficits with Novel Object Recognition (NOR) and Novel Place Recognition (NPR) and tissue is immunohistochemically processed to analyze tau levels and cellular morphology in TdTomato-labelled DG neurons. We assess synaptic changes in DG neurons

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via measuring dendritic spines, dendritic complexity and mossy fibre boutons. Preliminary findings show a trend for tau animals to perform worse on NOR compared to healthy controls, while no difference found for NPR. Morphological results show adult-born neurons have an increase in immature thin dendritic spines and decrease in mushroom spines (mature, functional spines) in tau animals relative to healthy controls, as well as reduced mossy fibre bouton filopodia length. Our initial results demonstrate the effect of tau on the LEC-DG circuit, with altered synaptic connectivity and memory performance.

3-C-357: RNA binding of heterogeneous nuclear ribonucleoprotein A1 is dysregulated in a mouse model of Multiple Sclerosis

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Neurodegeneration (NDG), hallmarked by neuronal cell body and axonal loss, occurs in progressive Multiple Sclerosis (MS) in the absence of overt relapses and inflammatory episodes. Heterogeneous nuclear ribonucleoprotein A1 (A1) is an RNA binding protein that is key in cellular RNA metabolism, but is mislocalized from nuclei to cytoplasm in the neurons from brains of people with progressive MS, and from spinal cords of mice with experimental autoimmune encephalomyelitis (EAE), a model for MS. We hypothesized that this mislocalization impacts the A1 RNA binding profile to promote NDG. To test this, we compared the A1 RNA binding profile from the spinal cords of naïve mice to those of mice with EAE, using crosslinking-immunoprecipitation/RNA sequencing (CLIPseq). We confirmed that the global RNA transcriptome from EAE mouse spinal cords is distinct from that of naïve mice, and further found that severity of EAE disease resulted in a greater alteration in the global transcriptome, with a number of differentially-expressed genes involved in neurodegeneration. We have also generated a first-of-its-kind profile of homeostatic A1 RNA targets in spinal cord. Further, the A1 RNA binding profile is drastically dysregulated in EAE mouse spinal cords, losing interaction with ~40% of homeostatically bound RNAs and instead enriching for non-coding RNAs. We are in the process of mapping the A1 binding "footprint" on these RNAs to provide insight into its specificity. Together, these data will form the foundation of our understanding of the role A1 dysfunction plays in NDG in MS.

D - Sensory and Motor Systems

3-D-360: Using novel rodent models of audiovisual perception to assess the influence of prior sensory exposure on audiovisual perceptual judgments

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To provide us with a complete sensory experience, our brain naturally merges information from our various senses (e.g., vision and hearing). The brain's ability to integrate auditory and visual information is not static; studies have shown that recent sensory experience can influence the accuracy and sensitivity of one's perception. To better understand the neural mechanisms underlying this process, we set out to develop and validate rodent models of audiovisual temporal and synchrony perception. Rats were trained on one of two perceptual

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judgment tasks: (1) a temporal order judgment (TOJ) task where rats reported whether the auditory or visual stimulus was presented first, or (2) a synchrony judgment (SJ) task where rats reported whether the auditory and visual stimulus were presented at the same moment in time or different times. To test for sensory adaption, rats were passively exposed to either synchronous or asynchronous stimuli prior to undergoing an experimental test session. Consistent with human studies, both tasks showed a psychophysical relationship between stimuli timing offsets and performance. Interestingly, prior disclosure to asynchronous audiovisual stimuli resulted in a shift of the psychophysical curve in the direction of the stimulus offset in rats performing the TOJ task, but not the SJ task. Additional testing is underway using the SJ task to further investigate synchrony perception in rats. Our collective results suggest that rats represent a suitable model for future studies aimed at studying the neural mechanisms underlying audiovisual perception.

3-D-361: Combining two photon microscopy and pupillometry to analyze sleep stage specific activity patterns in the mouse retrosplenial cortex

Brian Marriott[1], Jesse Jackson[1]

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The retrosplenial cortex (RSP) is an elongated midline cortex in rodents that has roles in spatial memory encoding and consolidation due to connections with the hippocampal formation. It is hypothesized that the RSP is involved in generating the mental imagery of dreaming during rapid eye movement sleep (REM). However, it is unclear how the spatiotemporal structure of neural activity in the RSP changes across REM episodes and how neural activity patterns are altered by experience. We trained mice to sleep under a two-photon microscope, which enabled the repeated imaging of a consistent and stable field of view of cells through an implanted gradient index lens, and collect neural activity from the RSP during REM, slow wave, and waking epochs separated by up to two weeks. By combining two photon calcium imaging with calcium sensors such as jGCAMP8f and synchronized pupillometry, we provide data in mice showing how RSP cells are active across these brain states, and how their activity is correlated with pupil movement and changes in sleep-wake behavior. Preliminary data indicates the presence of both REM-active and pupil-movement-active RSP cells. Future directions include perturbing the inputs to the RSP in order to observe the network connections responsible for generating brain state dependent neural activity patterns.

3-D-362: Probing the cerebellar contribution to aging using chemogenetics

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Declines in motor coordination are common in aging and limit a person's quality of life. The cerebellum is critically involved in motor coordination. Cerebellar Purkinje cells fire spontaneous action potentials at high frequencies, which is disrupted in several animal models of ataxia. Rescuing Purkinje cell firing rate deficits in mouse models of ataxia has been shown to improve motor coordination, suggesting that high frequency firing of Purkinje cells is important for normal cerebellar function. We wondered whether cerebellar alterations contribute to aging-related motor decline. To address this, we measured motor coordination in healthy C57Bl/6J mice across their adult lifespan, from young to old adult, and observed a

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progressive age-related decline. We then performed loose cell-attached recordings from Purkinje cells to measure spontaneous action potential firing in acute cerebellar slices. We observed an age-dependent reduction in Purkinje cell firing rates, suggesting that Purkinje cell firing might contribute to the decline in motor coordination we observed. To determine whether Purkinje cell firing alterations directly contribute to motor dysfunction in aging, we used viral delivery of chemogenetic receptors to modulate Purkinje cell action potential activity. We found that chemogenetically reducing Purkinje cell firing rates led to a decrease in motor coordination in young mice, suggesting that Purkinje cell firing output directly modulates motor coordination. Our data suggest that aging-related Purkinje cell firing deficits contribute to declining motor coordination observed in aging individuals.

3-D-363: Afferent input "re-organization" after a complete thoracic spinal cord injury in rats

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Introduction: Rats with complete spinal cord injury (SCI) exhibit good plantar stepping in the upright posture 5weeks after complete SCI without any training. Spontaneous reorganization of spinal circuits transmitting afferent input from the sole of the foot via the Tibial nerve (TIB) is a main contributor to this locomotor recovery. The purpose of this study was to examine changes in afferent pathways of the TIB at different times after SCI. Methods: Cord dorsum potential responses to graded electrical TIB stimulation were measured in 17 rats at different levels of the lumbar spinal cord. Intra-spinal field potentials were recorded (6 rats) after graded TIB stimulation. The amplitude of the different components of these potentials were normalized and compared in rats with intact cords (x), injured cords at 1 week (y) and at 5 weeks (z) post SCI. Results: The TIB group I muscle afferents evoked maximal response at the L4-L5 level in both intact and spinalized animals. The group II muscle afferents evoked surface potentials that decreased at L4 at 1 week after SCI compared to responses in intact rats. By 5 weeks post SCI, the group II responses became similar to those seen in the intact rats coinciding with upright walking development. Intraspinal field potentials from the dorsal horn also showed a similar reduction and recovery pattern. Conclusion: The reduction observed in cord dorsum and intraspinal field potentials evoked by group II afferent stimulation of the TIB at 1 week SCI suggests that dorsal horn interneurons with group II input are compromised at this time.

3-D-364: Modality matters: how inhibition shapes thermal and mechanical encoding in neuropathic pain.

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Our sensory system detects, discriminates, and sorts innocuous from noxious (i. e. nociceptive) stimuli according to their modality (heat, pinch, etc.) in different circuits of the spinal cord dorsal horn (SDH). Synaptic inhibition uses entry of Cl- to keep activity of those circuits in check. Low intracellular Cl- concentrations are critical to maintain robust inhibition

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under a high activity load, a task accomplished by the K+-Cl- cotransporter KCC2. Inability to control activity in nociceptive circuits leads to sensitization, a form of maladaptive plasticity contributing to pathological pain. It has been shown that neuropathic pain (i.e. pathological pain caused by an injury to the nervous system) is supported by a downregulation of KCC2. However, the extent to which this affects the different circuits of the SDH remains unknown. We have shown that KCC2 levels detected by immunohistochemistry vary between superficial and deeper circuits of the SDH encoding heat and mechanical nociception, respectively. Knowing this, our hypothesis is that inhibition differently shapes mechanical and heat nociception in normal and neuropathic conditions. Using electrophysiology, optogenetics and behavior, we have shown that mechanical circuits are more resistant to sensitization than heat circuits due to higher levels of KCC2. However, we have shown that mechanical circuits are more affected by the KCC2 downregulation accompanying neuropathic pain. This study will broaden our understanding of the implication of KCC2 in the different symptoms of neuropathic pain.

3-D-365: Investigation of periaqueductal gray circuitry in larval zebrafish

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As animals move through their environment, they work towards their goals and to avoid danger. If an animal detects a threat, it must decide on an appropriate response. The responses appear different between animals; however they all aim to increase the organism's chance of survival. The neural structures involved in these decisions and responses are so crucial that they are present in organisms across the animal kingdom. One such structure is the periaqueductal gray (PAG), found in the vertebrate midbrain. It is essential for any behavioural response to threatening stimuli, but due to its location deep in the brain, simultaneous investigation of the entire PAG has proved challenging. Larval zebrafish offer an excellent opportunity for in vivo imaging of the entire PAG due to their small size, optical accessibility, and the genetic tools available to researchers. To investigate PAG functional activity in the larval zebrafish brain I have created an experimental setup which allows for simultaneous presentation of visual stimuli, and observation of animal behaviour and neuronal activity. Additionally, I have developed an analysis pipeline for unsupervised clustering of neurons based on their activity to identify behaviour induced shifts in patterns of activity. I have identified a region in the midbrain which exhibits sustained activity in response to threatening stimuli and stains for canonical markers of the PAG, namely rln3 and penkA. Further investigation of this region will provide a more comprehensive understanding of how activity of the entire PAG affects behaviour.

3-D-366: Gaze behaviour with height-induced postural threat

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Background: Less exploratory gaze behaviour has been reported in individuals with visual height intolerance (vHI) compared to controls standing at high heights (Kugler et al., 2014); however, it is unclear if this gaze behaviour persists with different gaze conditions and how this compares to non-threatening settings. Therefore, this study aimed to investigate

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changes in gaze behaviour between low and high heights in individuals without vHI. We hypothesized less gaze exploration under conditions of postural threat. Methods: 14 healthy young adults without vHI (5 F; mean age=25) stood on a forceplate for 5 minutes at low (0.8m) and high (3.2m) heights facing a featureless canvas 2.6m away. Eye movements normalized to eye level and center of view were measured with a Dikablis eye-tracking system and used to calculate mean position and variance of gaze and number and duration of fixations and saccades. Results: Repeated measures ANOVAs revealed significant changes in postural and emotional-cognitive outcomes. Number of fixations ($p<0.05$, $\eta^2p=0.27$) and saccades ($p<0.05$, $\eta^2p=0.31$) significantly decreased with height. There were non-significant trends for increased fixation length and decreased saccade amplitude with increased height ($\eta^2p=0.20$; 0.14, respectively). Likewise, there were non-significant trends for decreased horizontal variance and lower mean gaze position with increased height ($\eta^2p=0.19$). Conclusions: Individuals without vHI demonstrated less gaze exploration under threatening conditions, characterized by fewer and longer fixations within a smaller horizontal area.

3-D-367: A retrospective investigation of short- and long-latency afferent inhibition data from six years of published studies

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Short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI) occur when the motor evoked potential (MEP) elicited by transcranial magnetic stimulation (TMS) is reduced by the delivery of a preceding peripheral nerve stimulus. However, the intra-individual variability in these measures is significant, and normative values would facilitate the interpretation of SAI and LAI in future studies. In the present analysis, we pooled data from studies published by our lab between 2014 and 2020. We present individual data from each study and investigate patterns in the depth of inhibition with respect to age, biological sex, and time of testing. Further, we quantified the reliability of the data for studies with repeated baseline SAI and LAI measurements. Our data show no relationship between the depth of inhibition for SAI and LAI with either time of day (SAI: rho = 0.089, p = 0.280; LAI: rho = 0.152, p = 0.102) or age (SAI: rho = -0.003, p = 0.973, n =113; LAI: rho = 0.095, p = 0.398, n = 81). Further, there was no significant difference in SAI or LAI between males and females ($p > 0.05$). Intra-class correlation coefficients (ICC) for repeated measurements of SAI and LAI ranged from moderate (ICC = 0.523) to strong (ICC = 0.882). This retrospective study explores normative values and reports the reliability of these measures as assessed in our lab with the goal of facilitating the interpretation of SAI and LAI data.

3-D-368: Visuomotor coding in single versus multi-unit activity of the monkey frontal cortex

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Multi-unit (MU) activity, the average firing of several simultaneously recorded neurons, is being increasingly studied because it is relatively easy to obtain and may represent subpopulation coding of a stimulus. Here, we examined the spatial structure embedded in

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the simultaneously recorded MU activity of the frontal (FEF) and supplementary eye field (SEF) neurons, compared to a previously published single-unit (SU) dataset (Bharmauria et al. 2020, 2021). The spiking activity (visual, memory, and motor) was recorded during a memory-guided cue-conflict saccade task (where a target-fixed landmark shifted during the delay) by head-unrestrained monkeys (Macaca mulatta). Then, by rethresholding raw neuronal data, MU activity was isolated. To determine if MU activity carries the same information as SU activity, a model fitting approach was used on MU response fields along a target (T) to gaze (G) continuum. Like SU activity, at the same sites: 1) MU visual (FEF=88; SEF=45) and motor (FEF=90; SEF=49) activities coded for target-in-eye and future gaze-in-eye coordinates, respectively. 2) There was a progressive transition from T to G coding along the spatiotemporal domain (spanning visual-memory-motor activity). The MU activity of FEF motor neurons better predicted G than SU activity ($p<0.05$) but missed some details of the temporal transformation. These results suggest that MU activity is a reliable indicator of the major features of sensorimotor transformations with potential for translational purposes in medical settings. Supported by CIHR, NSERC USRA and the VISTA Program.

3-D-369: The role of descending pathways in population coding of 2nd order electrosensory stimuli

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It has been shown that the nervous system implies descending pathways to efficiently encode sensory input of low contrast natural stimuli. However, the underlying mechanisms and their impact on perception and behavior remain poorly understood. Here we investigate the effects of descending pathways (feedback) on population coding and perception of 2nd order stimuli ("envelopes") within the hindbrain of the weakly electric fish Apteronotus leptorhynchus. These fish constitute an excellent model system for studying these important questions as our previous work has shown that descending pathways mediate the perception of low contrast sensory input. Here we will instead ask whether such mechanisms also apply to higher contrasts. To do so, we used envelope stimuli with different frequencies as well as intensities and tested behavioral responses while simultaneously recording from a population of sensory neurons. We then blocked feedback and compared behavioral and neural responses. Preliminary results show that while behavioral responses could be reduced by blocking feedback, neuronal responses remained similar at high but not low contrasts. This suggests that for low contrasts changes in behavior can be explained by feedback mechanisms, whereas this is not the case for high contrasts. This leads to the question as to the mechanisms in downstream brain areas and what decoder can explain this discrepancy. Our results thus can uncover mechanisms underlying coding and consequences on perception of stimuli with different statistics that are likely to be shared across sensory systems and across species.

3-D-370: A role for a persistent subthreshold K+ current in generating rhythm within larval zebrafish spinal locomotor circuits

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Spinal locomotor circuits have the intrinsic capability of producing the rhythmic activity needed to underlie repetitive locomotor movements. Locomotor rhythm generation can be shaped by the specific ionic conductances that spinal neurons express. Since the emergence of the larval zebrafish as an attractive vertebrate model to the study of locomotion, appreciable progress has been made in uncovering the cell types and connectivity patterns that make up zebrafish spinal locomotor circuits; however, little is known regarding their mechanisms for locomotor rhythm generation. IM, a persistent subthreshold potassium current, has been demonstrated to be involved in regulating neuronal bursting and recent evidence demonstrates that it is involved in locomotor rhythm generation in the neonatal rat. We sought out to determine whether IM could be involved in shaping the locomotor rhythm in larval zebrafish which, to our knowledge, has remained uninvestigated. Our ex vivo electrophysiological recordings of motor nerves during spontaneous swimming activity of 4 days post fertilization larvae in the presence of ICA-069673 and XE-991 - agonist and antagonist, respectively, of the IM-mediating Kv7.2/7.3 channels - reveal that IM may limit the amplitude and promote rhythmicity of tails beats produced during swimming activity. These findings further detail the mechanisms by which locomotor rhythm generation is governed in the larval zebrafish, highlighting that the role IM plays in locomotor rhythm generation may be similar across species.

3-D-371: The coordination of thermoregulation by circadian and thermosensory mechanisms

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The ability of organisms to sense and respond to temperature in their ambient environment as well as in their own bodies is critical for survival. Thermoregulation occurs as an essential homeostatic process Currently there exists a paucity of information on the involvement of the afferent mechanism of thermoregulation in ectotherms. Here we investigate thermoregulation and the involvement of a family of thermosensing proteins known as the transient receptor potential (TRP) channels in the ectotherm Xenopus laevis. Using Xenopus larvae as an in vivo model, and a melanophore cell line as an in vitro model, our data indicate that within skin melanophores pigments known as melanosomes aggregate in cool temperatures and disperse at warmer temperatures. Our in vivo model suggests that this aggregation of skin pigments occurs as a systemic response. We identified TRP family genes in the Xenopus genome via RT-PCR, including a candidate (TRPM8) from the TRPM subfamily, which has been characterized previously as a cold sensor. Using immunohistochemistry, we visualized TRPM8 expression in Xenopus melanophores and the skin, and found that TRPM8 is co-localized with melanophores using a melanophore-specific marker. To investigate the function of TRPM8, we treated cultured melanophores and Xenopus larvae with an agonist (WS12), which resulted in aggregation of pigment in the absence of cool temperature. Our results suggest that in Xenopus larvae temperature alterations regulate skin pigmentation, a process that depends on a member(s) of the TRPM channel family. (Support from the Natural Sciences and Engineering Research Council, Canada)

3-D-372: The effect of self-motion on electrosensory inputs

Mary Upshall[1], John Lewis[1]

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Weakly electric fish actively sense their environment using a self-generated electric field. Objects with electrical properties differing from those of the surrounding water cause small perturbations that are detected by electroreceptors distributed over their skin surface. When sensing conditions are unfavourable, fish appear to increase several movements (tail-bending and back-and-forth swimming) that are thought to improve electrosensory acquisition. However, these movements are variable and not reliably identified. Recently, unbiased data-driven approaches have been used to extract fundamental poses, combinations of which can be used to describe any animal behaviour. Here, we apply these approaches as a first step towards testing the hypothesis that specific movements can enhance electrosensory information acquisition. We find that fish behaviour can be explained by combinations of only a few fundamental basis shapes. Then, along with a newly developed model for quantifying the electric field, we characterize the spatiotemporal properties of natural electrosensory inputs and identify how they are affected by body pose and movement.

3-D-373: Whole-brain optical imaging in zebrafish larvae to investigate neural circuit development and connectivity

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To learn more on the factors that govern the development of neural circuits, both in structural and functional terms, we use whole brain two-photon imaging on larval zebrafish that express a pan-neuronal genetically-encoded calcium indicator GCaMP6s. Using a resonant scanner and piezo driven objective, we record neural activity (GCaMP6 fluorescence) from up to ~50% of the whole neuronal population (~100,000 neurons), while simultaneously conveying visual stimulation using a screen oriented towards the head-restrained larva in agarose. This experimental paradigm leverages the early-developing visual system of the zebrafish to evoke reproducible neuronal responses and behavioral outputs across individuals. Abrupt changes in illumination induce navigational tail movements, which are monitored using a high-speed camera to identify distinct behavioral modules and their neural correlates. By varying the temporal properties of visual stimuli, we also probe the neural mechanisms of habituation and anticipation. Using graph theory, functional networks are generated from spontaneous brain activity recordings, which are then paired with the zebrafish structural connectome (Kunst et al., Neuron, 2019) in order to gain fundamental insight on the interaction between structure and function in vertebrate brain networks. Our dual spontaneous/stimulus-evoked experimental framework will be used to compare fish across different developing conditions, namely germ-free fish, to observe the impact of gut microbiota on brain connectivity, sensorimotor integration and behavior.

3-D-374: Cortical Mechanisms for reach-grasp integration: an fMRI study

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The cortical mechanisms for reach and grasp are well understood, but mechanisms that integrate these two components are not yet established. Here, we used functional magnetic

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resonance imaging (fMRI) to investigate the integration of reach and grasp instructions into the movement plan using a cue-separation paradigm. Twelve participants were asked to grasp vertically or horizontally a cubic object presented to their left or to their right for this task. Their grasping movement onset was preceded by two successive cues, either a visual cue of the target location or an auditory cue of the target orientation. Each cue presentation was followed by a delay period. Whereas the first delay period only required participants to remember one cue, the second delay period required participants to remember two cues and integrate them as they prepare to initiate the reach-and-grasp movement. Tentative univariant results revealed the different cortical processing of the visual vs. auditory cue in the first delay. A simple conjunction analysis between the two task orders in the second delay revealed activities in motor-related areas such as the Cerebellum and Dorsal Premotor, Supplementary Motor, Primary Somatosensory Cortex, and Cingulate and Insula. Removal of the influences of the visual and auditory cues in delay 1 refine the areas activated and confirmed their involvement in the integration. Our tentative interpretation is that insula and cingulate are involved in top-down integration of the task instructions, which are then combined within traditional motor planning areas. Supported by CIHR and the Vision: Science to Applications (VISTA) program.

3-D-375: Cortex-wide dynamics of norepinephrine release in resting state

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Resting state brain activity is characterized by ongoing fluctuations in neuronal activity that have widespread organization at multiple spatial and temporal scales. In mice, genetically encoded calcium sensors are proxies of neural activity, and allow the interrogation of large-scale population activity. At the cellular level this neuronal activity is bidirectionally related to neurotransmitter and neuromodulator release and clearance dynamics. The development of protein biosensors designed to measure specific neurotransmitters and neuromodulators enables the investigation of their dynamics on a sub-second timescale, as well as the relationship of these fluctuations to neuronal calcium activity at the mesoscale. Using combined imaging of the norepinephrine sensor GRAB_NE1m and the red-shifted calcium indicator jrGECO1a, we describe cortical mesoscale dynamics of norepinephrine release in awake head-fixed mice. AAV9-GRAB_NE1m was injected in three bilateral cortical sites in Thy-1 jrGECO1a mice, allowing combined imaging over a large expanse of the dorsal cortical surface (approximately 8x8mm) through a chronic intact skull preparation. After recovery and head-fixation training, GRAB_NE1m and jrGECO1a were simultaneously imaged using a dual camera setup with strobed excitation of GRAB_NE1m (470nm) and jrGECO1a (567nm), in addition to red and green wavelengths for hemodynamic signal correction. In spontaneous resting state, we find evidence for spatial and temporal dynamics in the cortical release of norepinephrine associated with neuronal calcium fluctuations.

E - Homeostatic and Neuroendocrine Systems

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3-E-376: Long-range hypothalamic neuronal projections to the subventricular zone neurogenic niche regulates neural stem cell function through endocannabinoid signaling

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The subventricular zone neurogenic niche receives neuronal inputs from many areas of the brain. Although these inputs are known to regulate neurogenesis through neurotransmitter release at synapse-like connections between neuronal axon terminals and neural stem and progenitor cells (NPCs), few studies have examined how neuronal modulators at these synapse-like connections affect SVZ NPC function. Our recent work identified monoacylglycerol lipase (Mgll), a hydrolase that breaks down endocannabinoid 2-AG, as an extrinsic factor to regulate SVZ NPC function in culture. 2-AG is a well-known retrograde modulator that controls neurotransmitter release. To date, it remains unknown how Mgll-modulated 2-AG signaling in the SVZ niche regulate SVZ NPC behavior in vivo. In this regard, we propose to examine the role of neuronal Mgll activity from distinct brain region in regulating SVZ NPC function. Using retrograde monosynaptic rabies virus tracing and anterograde tracing, we identified direct synapse-like connections between hypothalamic arcuate nucleus (ARC) neuron axon terminals and a subpopulation of NPCs residing in the ventral SVZ microdomain as previously reported. Intriguingly, specific removal of Mgll expression in ARC neurons using virally transfected Cre recombinase in Mgll-floxed mice resulted in a decrease of SVZ NPCs in this microdomain and a subsequent reduction of proliferating cells in this microdomain. These findings provide an understanding of how long-range neuronal Mgll activity regulates adult SVZ NPC function in a microdomain-specific fashion.

3-E-377: Anatomical organization of the rat subfornical organ

Amirah-Iman Hicks[1], Simona Kobrinsky[1], Suijian Zhou[1], Jieyi Zhang[1], Masha Prager-Khoutorsky[1]

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The subfornical organ (SFO) is a sensory circumventricular organ located along the dorsal part of the anterior wall of the third ventricle. SFO lacks a complete blood-brain barrier (BBB), and thus peripherally-circulating factors penetrate the SFO parenchyma. Circumventricular organs are characterized by the presence of unique populations of non-neuronal cells (tanycytes and fenestrated endothelium), however, how these populations are organized within the SFO is not well understood. In this study, we used histological techniques to analyze the anatomical organization of the rat SFO and examined the distribution of neurons, fenestrated and non-fenestrated vasculature, tanycytes, ependymocytes, glia cells, and pericytes within its confines. Our data show that the shell of SFO contains non-fenestrated vasculature. Fenestrated capillaries are restricted to the medial-posterior core region of the SFO, associated with a higher BBB permeability, and are encased in a scaffold of pericytes and tanycytes. Hypertonic NaCl activates SFO neurons located in the shell, while the location of angiotensin II-sensitive neurons varies between sexes. Our study provides a comprehensive description of organization of diverse cellular elements within the SFO, facilitating future investigations in this important brain area.

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3-E-378: Cell proliferation in the OVLT and SFO is altered in a model of salt-dependent hypertension

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Circumventricular organs (CVOs) are specialized brain regions characterized by a high density of fenestrated blood vessels, thus lacking a complete blood-brain barrier. The organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO) are sensory CVOs involved in the regulation of body fluid homeostasis and cardiac function. Recent studies reveal that secretory CVOs (the median eminence and the adjacent arcuate nucleus) harbor neural stem cells in the adult brain. However, it remains unknown if sensory CVOs such as the OVLT and SFO also have neural stem cells. To study if cells in the OVLT and SFO undergo constant cell proliferation in the adult brain, we intraperitoneally injected Wistar rats with the mitotic marker bromodeoxyuridine (BrdU) and used immunohistochemistry to visualize new-born cells. We have identified NG2 glia, tanycytes, pericytes and microglia that undergo constant proliferation in adult rats. Moreover, a small fraction of BrdU-positive cells expressed a neuronal fate marker, doublecortin. To examine if cell proliferation is attenuated in conditions with disrupted fluid balance, we subjected rats to a model of salt-dependent hypertension. Rats were exposed to a salt-loading protocol that replaces drinking water with 2% of NaCl for 7 days, leading to an increase in blood pressure. We found an increase in the number of BrdU-positive cells in the OVLT and SFO of rats exposed to 7 days of salt-loading. These data suggest that cells in the OVLT and SFO can undergo constant cell proliferation and might represent an additional neurogenic niche in the adult rat brain, and hypothalamic cell proliferation is altered in response to perturbation in fluid balance.

3-E-379: Melanin-concentrating hormone mediated inhibition of lateral septum neurons

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Melanin-concentrating hormone (MCH) is produced in the lateral hypothalamus. It has important roles in homeostatic and motivated behaviour. As MCH projections and receptors are widely distributed, the brain regions underlying MCH functions are not well understood. We showed that MCH neurons send dense projections to the lateral septum (LS) and innervate LS neurons by glutamate release. Consistently, retrograde injections into the LS showed that MCH neurons that innervate the LS are largely distributed medial to the fornix. However, it is not known if MCH can regulate the activity of LS neurons. In order to characterize MCH action in the LS, we first mapped the distribution of MCH-immunoreactive fibers and MCH receptor mRNA (Mchr1) throughout the LS. We observed the highest expression of both MCH fibers and Mchr1 toward the lateral and ventral borders of the intermediate subregion of the LS, and we selected LS cells for whole-cell patch clamp recordings from these regions. Bath application of MCH directly hyperpolarized LS neurons and elicited a membrane current that reversed at the equilibrium potential for chloride ions. This MCH-mediated hyperpolarization and current were blocked by the GABAA receptor antagonist bicuculline and indicated that GABAA-dependent mechanisms underlie the inhibitory actions of MCH in the LS. By contrast, MCH does not alter the frequency of

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glutamatergic or GABAergic input to LS neurons. In aggregate, the postsynaptic actions of MCH in the LS suggests that in addition to glutamate, MCH neurons may also regulate the LS by MCH release.

3-E-380: Investigating the effects of acute olanzapine exposure on central leptin actions

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Second-generation antipsychotics (SGAs) are the cornerstone treatment for schizophrenia, but their use is associated with severe metabolic side effects and increased appetite which may be due to disrupted actions of leptin (LEP) in the brain. We aimed to investigate the ability of olanzapine (OLA), a widely used SGA, to impair hypothalamic LEP mediated regulation of fuel preference and food intake. Healthy, male, Sprague Dawley rats received an acute intracerebroventricular (ICV) infusion of LEP (3 µg) or vehicle to the third cerebral ventricle along with an acute peripheral injection of OLA (2 mg/kg) or vehicle at the start of 12-h light and dark cycles. Metabolic parameters were recorded using indirect calorimetry apparatus for 24-h. OLA treatment rapidly reduced respiratory exchange ratio (RER), a measure of fuel preference, in light and dark cycles. This was followed by renormalization in the light cycle. ICV-LEP infusion resulted in a gradual but sustained reduction in RER in both light and dark cycles. LEP and OLA co-administration reduced RER in light and, most notably, dark cycles. Importantly, ICV-LEP significantly lowered food intake in the dark cycle regardless of OLA treatment. In conclusion, acute OLA and LEP exposure promote fat oxidation in light and dark cycles. In contrast to OLA, ICV-LEP mediated reduction of RER is a physiologically appropriate response to lower food intake. Furthermore, acute OLA does not appear to impair the hypophagic effect of ICV-LEP. Future research can elucidate possible OLA-induced impairment of peripheral LEP actions.

3-E-381: Neurochemical characterization of melanin-concentrating hormone neurons in the mouse lateral hypothalamus

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Melanin concentrating hormone (MCH) is an orexigenic neuropeptide located in the lateral hypothalamus. Cells expressing MCH are heterogenous and can be marked by their coexpression of cocaine- and amphetamine-regulated transcript (CART) or the neurokinin 3 receptor (NK3R). Transcriptomic studies show that one-third of MCH neurons coexpress both CART and NK3R. However, the distribution of this MCH subpopulation has not yet been mapped in the mouse brain. We determined the percentage of MCH neurons that coexpress CART and/or NK3R and mapped their distribution to Allen Reference Atlas mouse brain templates. We identified MCH neurons by native EGFP fluorescence (EGFP-f) in Mch-cre;L10-Egfp mice and then labeled CART and NK3R immunoreactivity. We found that 96% of EGFP-f cells were MCH-positive. Within the lateral hypothalamus, EGFP-f cells may be clustered medial or lateral to the fornix. Nearly half (49%) of the EGFP-f cells counted expressed EGFP-f only and were most commonly found lateral to the fornix. In contrast, 47% of EGFP-f neurons coexpressed CART, and these cells were more common medial to the

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fornix. Of the CART-positive EGFP-f cells, half of them also coexpressed NK3R, which appeared evenly throughout the lateral hypothalamus. Lastly, 4% of EGFP-f neurons coexpressed NK3R only. Our results indicate a robust heterogeneity within MCH neurons, and we will expand our analysis to determine if these MCH subpopulations also express distinct electrical fingerprints based on their neurochemical properties.

3-E-382: Spatial distribution of melanin-concentrating hormone receptor 1 in the ventral tegmental area

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Melanin-concentrating hormone (MCH) activates MCH receptor 1 (MCHR1) to promote positive energy balance. MCH or MCHR1 deletion, in part at GABAergic cells, leads to a hyperdopaminergic state and hyperactivity, as MCH can inhibit dopamine release. Here we assessed if MCH can directly regulate dopaminergic or GABAergic neurons in the ventral tegmental area (VTA). We labelled mouse Mchr1 mRNA by RNAscope in situ hybridization throughout the VTA and quantified its expression on putative dopaminergic or GABAergic cells by colocalization with tyrosine hydroxylase (TH) immunoreactivity or Slc32a1 (Vgat) mRNA hybridization, respectively. Half of all Mchr1 cells expressed TH, which comprised 25% of TH VTA cells, while only 13% of Mchr1 cells expressed Vgat, which represented 13% of Vgat VTA cells. We then mapped the expression of Mchr1 in TH and Vgat VTA neurons onto Allen Reference Atlas brain templates to assess their spatial distribution. Mchr1 expression was most prevalent in the posterior VTA (Bregma -3.28 mm to -3.68 mm) and concentrated within the medial aspect of the VTA. Vgat expression and its colocalization with Mchr1 increased in more posterior levels but TH and Mchr1 colocalization was relatively higher posteriorly. Interestingly, 36% of Mchr1 cells were neither TH nor Vgat positive, and future experiments will determine if they may be glutamatergic VTA cells. Importantly, we provide evidence for Mchr1 expression in the VTA and provide the basis for electrophysiological recordings to assess MCH-mediated action at TH and Vgat VTA cells.

F - Cognition and Behavior

3-F-383: The role of GABAergic inhibition in object category recognition

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Object category recognition and discrimination may rely on the use of generalized category representations formed through exposure to various category exemplars. Presumably, to refine category representations, extraneous object features must be inhibited. Parvalbumin-containing GABAergic interneurons (PVINs) have been implicated in visual stimulus learning, including the inhibition of irrelevant stimuli. To determine the role of GABAergic transmission in the refinement of object category representations, C57/BL6 mice were administered a GABAA receptor antagonist (bicuculline) prior to exposure to various category exemplars. When tested on a rodent object category recognition (OCR) task, mice administered

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bicuculline failed to perform a 1-h retention delay which requires pre-exposure to category objects. Then, to specifically examine the role of GABAergic PVINs in the perirhinal cortex (PRh), a region necessary for object recognition, we infused male PVcre mice intracranially with adeno-associated virus containing inhibitory designer receptors exclusively activated by designer drugs (DREADDs) to control the activity of PVINs in the PRh. The DREADD agonist 21 (11-(1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine; C21) was administered systemically prior to exposure to object category exemplars. Mice administered C21 prior to pre-exposure sessions were not able to perform the OCR task with the 1-h retention delay. Thus, GABAergic transmission, and specifically PVIN activity in the PRh, may play an essential role in the refinement of object category representations.

3-F-384: Cognitive impairments in mice after targeted perineuronal net depletion in the medial prefrontal or retrosplenial cortex.

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Perineuronal nets are highly organized components of the extracellular matrix which inhibit cellular plasticity and support cellular function. Depletion of perineuronal nets in rodents via developmental models of disease or via direct pharmacological interventions (e.g. chondroitinase) can impact cognitive function. In our current study, we utilized injections of an immune-evasive dual vector system, where the chondroitinase gene is under a doxycycline regulatory control, to induce bilateral secretion of chondroitinase, with temporal control, in the medial prefrontal cortex and retrosplenial cortex. These two brain regions are known to be involved in the function of working memory. We subjected mice to 30 days of activated chondroitinase-expression to deplete their perineuronal nets, followed by 30 days without to allow for a window of recovery. Prior to treatment, after treatment, and after 30 days without doxycycline-induced chondroitinase expression, animals were tested in a cross-modal object recognition task and an oddity task, which have been shown to be sensitive to manipulations of the medial prefrontal and retrosplenial cortex. Preliminary data indicates that controlled depletion of perineuronal nets in the medial prefrontal and retrosplenial cortex impacts performance of working memory. While there is some recovery in their working memory performance after 30 days without continuing enzymatic depletion, they do not recover to baseline behavioural performance. This data suggests that perineuronal net degradation in the medial prefrontal and retrosplenial cortex impacts working memory performance, and that these changes are long-lasting.

3-F-385: Value vs prediction error: The role of VTA DA transients in associative learning.

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Phasic firing of ventral tegmental area (VTA) dopamine (DA) neurons is recognized as a prediction error signal that supports learning about reward. Whether the signal drives learning through an error mechanism per se or by regulating value is hotly debated due to the difficulty in isolating changes in value from prediction error. We addressed this long-standing debate using optogenetic activation of VTA DA neurons in a series of blocking experiments, which isolate the role of prediction error in learning. Each experiment consisted

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of a conditioning phase followed by a blocking phase and a manipulation-free test. In the first experiment, we tested whether activation of DA neurons at the time of reward delivery during blocking reinstates learning about the normally blocked stimulus. We found that learning is unblocked to the level of a non-blocking control stimulus. To determine whether activation of DA neurons unblocks learning by boosting the value of rewards or by directly encoding error, we delivered identical stimulation across the two training phases (i.e., conditioning and blocking). If boosting the VTA DA signal unblocks learning by increasing prediction error through increases in value, then we should find blocking. If the signal unblocks learning by acting on prediction error per se, then we should find unblocking. We optogenetically boosted the VTA DA signal at time of reward delivery across both phases. We found that learning was unblocked to the level of a control stimulus. These data reconcile that DA firing in the VTA functions directly to encode error.

3-F-386: Intermittent versus continuous cocaine self-administration enhances the conditioned reinforcing properties of cocaine-associated cues in rats

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Human cocaine use is typically intermittent, both within and between bouts of use, but most drug self-administration studies in laboratory animals involve continuous drug intake. Intermittent cocaine use produces spikes in brain drug levels and promotes addiction (Allain et al., 2015). Beyond direct drug effects, cocaine-paired cues also contribute to addiction. Such cues can acquire incentive motivational value, enabling them to trigger and invigorate cocaine use. Here we determined in rats whether cues paired with intermittent vs continuous cocaine intake acquire more motivational value. Rats were assigned to self-administer i.v. cocaine under either intermittent-access (IntA; 5 min cocaine ON and 25 min OFF, for 4 h) or continuous-access conditions (CONT; cocaine ON for 4 h), for 10 sessions. Each drug infusion was paired with a 25-s light-tone cue. Control rats received 70 cue presentations/session, without cocaine, to assess any intrinsic behavioural effects of the cue. After the 10 sessions, all rats could press a new lever to receive cue presentations alone, without cocaine. Both CONT and IntA rats pressed more on the lever than control rats did, and IntA rats pressed more for the cue than CONT rats did, indicating increased conditioned incentive motivation. IntA rats (but not CONT rats) also lever pressed for the cue 30 days after the last cocaine self-administration session, indicating persistent motivational effects. Thus, discrete cues paired with intermittent vs. continuous cocaine use acquire greater and more persistent incentive motivational value.

3-F-387: Exploring the effects of prior stressor experience and vicarious stress in juvenile and adult female rats

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Vicarious stress occurs when witnessing others undergo trauma and can be modeled in rodents. Prior stressor experience in witnesses may be required to enhance vicarious stress. Most studies utilize adult animals however less is known about vicarious stress in juveniles. We explored and compared the behavioural effects of vicarious stress and prior stressor

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experience in juvenile and adult female rats. Four witness groups were included: Control (no experience, no vicarious stress), Context (experience, no vicarious stress), Naive (no experience, vicarious stress), and Experienced (experience, vicarious stress). Experienced and Context groups were subjected to ten 1.0 mA footshocks over 12 minutes. On the next day, Naive and Experienced groups watched their cagemate endure footshocks from a perforated transparent barrier. Control and Context groups watched the cagemate roam freely. Fear expression was measured 24hrs after and social interactions and acoustic startle response were recorded. There were no age differences in Experienced groups which had greater fear expression during the vicarious stressor. Adult Experienced groups had greater fear expression after 24 hours compared to juveniles. There were no effects of vicarious stress and experience on the social interactions and acoustic startle response, yet juvenile rats spent more time interacting and had a larger startle response. In sum, prior stressor exposure was required for vicarious stress to increase fear expression acutely in adult and juvenile female rats yet led to unchanged behavioural responses.

3-F-388: Investigating the effect of THC vapour exposure on stress reactivity in rats following an acute stressor

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Management of stress and anxiety is often listed as the primary motivation behind cannabis use, yet the understanding of how acute exposure to cannabis modulates the neurobehavioral and endocrine response to stress is not well characterized. As inhalation is the primary form of consumption in humans, modelling this approach in rodents is important given the robust impact of route of administration has on the pharmacokinetics of THC and its metabolites. With advancements in drug delivery for rodent studies, basic science approaches can now be employed to better establish the impact of cannabis use on stress reactivity in a highly translational manner. The current study aims to examine the impact of acute, controlled passive delivery of THC on male and female rats to determine how this impacts neural and endocrine responses to acute stress. Thirty-two male and 32 female adult rats were exposed to vehicle vapour for 9 days. On day ten, rats were randomly assigned to one of two vapour conditions: 1) control; and 2) THC and one of two stress conditions: 1) naïve; and 2) stress (30 min restraint stress). The initial exposure to vehicle vapour increases cort levels in male and female rats; however, only males habituated to exposure by day 9. Acute exposure to THC immediately elevated cort levels in males but not females. The impact of THC vapour on neuronal activity using c-fos is currently underway. These data indicate that acute exposure to THC vapour is sufficient to produce elevations in the stress hormone cort in males but does not impact stress-induced changes in cort.

3-F-389: Pupil size anticipates exploration and predicts disorganization in prefrontal cortex

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To successfully navigate uncertain environments, we need an algorithm for exploration: a way to ensure that we sample policies whose value is uncertain. We also need a mechanism

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to reliably follow rewarding policies we discover: a system for exploitation. Understanding how exploration and exploitation are implemented in the brain is a major topic of research in decision-making neuroscience, with several studies pointing to pupil-linked mechanisms. However, these studies relied on ad hoc applications of reinforcement learning models that were not designed to identify exploration. As a result, it is still not clear whether pupil-linked mechanisms predict exploratory behavior per se, much less its neural signatures. Here we applied a novel approach that models exploration and exploitation as latent goal states generating decisions. This allowed us to contrast model-labelled explore and exploit decisions in terms of both (1) pupil size and (2) neural activity recorded in the frontal eye fields (FEF), a part of the prefrontal cortex implicated in sensorimotor decision-making. We found that pupil size was larger during exploration and ramped up in anticipation of exploration. Then, it abruptly decreased below baseline levels at the start of exploitation. Concurrently, pupil size predicted neural signatures of exploration in FEF neurons and neuronal populations. In sum, we found that pupil-linked processes anticipate exploration via disruption of neuronal tuning. Further research will be necessary to identify how exactly pupil-linked mechanism influence exploration.

3-F-390: Characterizing 'the munchies'; effects of tetrahydrocannabinol (THC) vapour inhalation on satiety and food preference in rats

Catherine Hume[1], Samantha Baglot[1], Matthew Hill[1]

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With cannabis use progressively increasing globally, there is an urgent drive to assess if cannabis has potential health-related effects. It is well known that cannabis acutely promotes food intake, commonly known as 'the munchies', and that tetrahydrocannabinol (THC), the main psychoactive cannabis component, is responsible for driving these effects. Previous rodent studies have merely modelled increased feeding following THC exposure; therefore, the aim of this study is to use a translational THC vapour inhalation rat model to characterize the effects of THC on satiety and food preference. Rats were exposed to THC or vehicle vapour for 15min, and subsequent food intake measured. To induce satiety rats were given a sucrose-chow mash to eat prior to vapour exposure. To measure post-vapour food preference, intake of a high-carbohydrate and a high-fat food was simultaneously measured. In satiated rats, THC vapour acutely increased regular chow intake and increased high-carbohydrate food preference. In non-satiated rats, THC vapour acutely increased high-fat food preference. We show that THC can override satiety mechanisms to drive food intake in the satiated state. Furthermore, THC alters food preference, however, the preferred macronutrient appears to be dependent on the state of the animal. This data sheds light on how cannabis use can disrupt homeostatic feeding patterns and potentially promote the consumption of 'unhealthy' high-fat or high-carbohydrate foods, information which is critical for the health and well-being of regular cannabis users.

3-F-391: Would short-term, indirect social stress affect spatial learning and memory in either male, or female rats?

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Objective: The purpose of our study was to determine whether indirect social stress could affect brain areas important for spatial learning and memory in adult rats. Methods: Each week for 10 consecutive weeks, 4 male and 4 female Sprague-Dawley rats were randomly assigned to same-sex pairs. Next, twice daily for 5 consecutive days, one male and one female rat were placed on an elevated platform for 30 min (Platform Stress, PS). The cage-mates of PS animals were considered members of the Bystander Stress (ByS) group (i.e., those receiving indirect stress). As well, Platform Control (PC) animals were simply moved to another room twice daily for 30 min, and the cage-mate of each PC animal was considered to be a Bystander Control (ByC). Spatial learning and memory were then assessed over 5 days using standard training and probe trials in the Morris water maze. The animals were then sacrificed and brain tissue harvested to allow for the assessment of differences in synaptic proteins. Results: Regardless of sex, there were no statistically significant differences among the ByC and ByS animals in either spatial learning [training day four: $F(3, 72) = 1.4$; $p = .24$], or memory [$F(3, 72) = 1$; $p = .17$]. Conclusion: Our results suggest that ByS may not dramatically affect spatial learning and memory in either male, or female rats. As our next step, we will analyse the synaptic expression and phosphorylation level of several plasticity-related proteins (e.g., GluN1, GluA2, PSD-95) in the hippocampus across the treatment groups.

3-F-392: Hippocampal theta rhythm modulation by the glutamatergic and serotonergic raphe

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Theta rhythms (4-12 Hz) are crucial for hippocampal network coordination and functions, including memory and anxiety. Lesion and pharmacological studies have shown that the median raphe nucleus (MR) exerts a strong modulation over theta rhythms. However, the MR is composed of mixed neuronal populations, including serotonergic neurons (5-HT) and glutamatergic neurons expressing the vesicular glutamate transporter type 3 (VGLUT3). In this study, we aim to evaluate the contribution of these two largely distinct median raphe neuronal populations to theta rhythm properties. We used optogenetics to activate either 5HT or VGLUT3 neurons in the median raphe (MR) of freely behaving mice. To do so, we injected CRE-dependent AAV vectors in the MR of either SERT-CRE or VGLUT3-CRE mice, to selectively transfect 5-HT or VGLUT3 MR neurons with the excitatory opsin ChETAET/TC. An optic fiber implanted above the MR allowed light delivery and activation of 5-HT or VGLUT3 neurons, while simultaneously recording theta rhythms in the hippocampus during REM sleep and awake locomotion. Our results show that 5HT and VGLUT3 neurons participate in the modulation of hippocampal theta frequency and power. These results suggest a potential role for MR 5-HT and VGLUT3 neurons in the modulation of hippocampal functions such as memory and anxiety.

3-F-393: Activity of hippocampal VIP interneurons during memory encoding in freely behaving mice

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Most of the hippocampal vasoactive intestinal polypeptide (VIP) expressing interneurons (INs) specifically target interneurons, providing a disinhibitory mechanism for ungating the external inputs onto excitatory neurons. CA1 VIP INs have been shown to aid spatial learning and memory but their role in memory encoding is yet unknown. To address this subject, first, we employed a series of behavioral paradigms and a unified paradigm to examine What-Where-Which episodic-like memory. Second, we simultaneously performed in vivo calcium imaging of CA1 VIP INs activity in freely behaving mice using wireless fiber photometry. We found that VIP INs were routinely active throughout the entire period of exploration with a mean calcium transients (CaTs) frequency of ~0.25 Hz. Examining VIP INs' activity during various behavioral states revealed distinct activity patterns and higher CaTs during grooming periods compared to object exploration and rearing periods. Additionally, grooming-associated CaTs showed a robust correlation with the duration of grooming. Furthermore, during exploration of objects, VIP INs' activity showed evenly balanced rising and dropping patterns, which evolved over the course of the object familiarization. Taken together, these results indicate that VIP INs encode certain aspects of behavioral states and spontaneous object exploration during memory encoding. Ongoing work using state-dependent optogenetic perturbations and analysis of VIP IN activity will help understand the contribution of disinhibitory circuits in spatial memory encoding and cognitive mapping.

3-F-394: Early life adversity and a sex-specific polygenic risk for fasting insulin are associated with variations in childhood executive functioning

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As insulin is an important hormone for childhood growth and development and has implications for adult psychopathology in both males and females, we hypothesized that 1) the genetic background associated with altered fasting insulin (FI) and ADHD would be shared; 2) if (1) is rejected, the genetic background associated with altered fasting insulin would perform better in interaction models, G by E (childhood adversity), as opposed to main effect models to predict child psychosocial problems and adult psychopathology. Using conjunctional false discovery rate (FDR), we saw that no SNPs were shared between the FI GWAS and ADHD GWAS. (2) We calculated polygenic risk scores (PRS) from the sex-specific FI GWAS at different thresholds and identified one that best predicted peripheral insulin levels in male and female children in the ALSPAC cohort, further refining it to only include SNPs significantly associated with the peripheral insulin levels (p-refined<0.05). As hypothesized, these PRS predicted childhood total problems and ADHD (CBCL) in children from the MAVAN cohort (76 females, 74 males), in pre-adolescents of the ABCD cohort (3684 females, 4037 males), as well as mood disorders in adults from the UK Biobank (44638 females, 26576 males) in a sex-specific manner at each age in response to childhood adversity. The genetic background associated with higher fasting insulin levels is linked to psychopathology, but this effect is dependent on the exposure to adversity. The findings reported here have implications for identification and treatment of psychopathology at different ages.

3-F-395: Tracing molecular and social pathways to sex differences in depression: An empirical analysis of the Canadian Longitudinal Study on Aging (CLSA)

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Variations in gene expression patterns and cortico-striatal circuit morphology have been linked to sex differences in depression. We investigated gene-by-environment (G*E) interactions between dopamine gene expression in these brain regions and the social environment on depressive symptomatology (CESD-10 scale) in 45-75 y.o. CLSA participants. We computed two biologically-informed genetic scores related to the D4 dopamine receptor (DRD4): 1. predicted prefrontal (PFC) expression using PrediXcan machine learning; 2. expression-based polygenic risk scores for the co-expression gene network in the striatum (STR-ePRS). Using latent profile analysis, we classified individuals based on social network size, support, cohesion, and participation in 3 distinct profiles: low-, medium-, and high-social network support (18/40/42%). In the full sample, G*E interactions were significant for STR-ePRS--with effects driven by men--but not for PFC expression. Analyses by sex revealed significant G*E effects for both DRD4 scores in men (n=7217) but not in women (n=6733). Lower STR-ePRS scores were associated with worse depressive symptomatology for men in the low-support profile. Higher PFC DRD4 expression was associated with worse depressive symptoms for men in the low-support profile but milder symptoms in the medium- and high-support groups. The DRD4 gene network overlapped with gene sets related to cardiometabolic health (blood pressure, BMI, diabetes), suggesting common pathways for physical and mental well-being. Our findings implicate DRD4 and related gene networks as potential moderators of social environmental influences in depression, particularly for male seniors with low social support, consistent with previously reported sex differences in reward sensitivity and decision-making.

3-F-397: Nicotine self-administration behavior under continuous versus intermittent access conditions in male and female rats

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Tobacco smoking is the main cause of preventable disease in Western Europe and North America. Nicotine is the principal psychoactive agent in tobacco, underlying tobacco's addictive properties. Most preclinical studies on the effects of voluntary nicotine use have used self-administration procedures that provide continuous nicotine access during each self-administration session (Long-access or LgA). However, many smokers consume cigarettes intermittently, rather than continuously throughout each day. Here we gave female and male rats LgA (6 h/day) or intermittent access (IntA; 12 min ON, 60 min OFF, for 6 h/day) to intravenous nicotine (15 µg/kg/infusion), for 12 daily sessions. We then compared the groups on intake, responding for nicotine under a progressive ratio schedule of reinforcement, as well as cue- and nicotine-induced reinstatement of nicotine-seeking behavior after abstinence (measures of relapse). Nicotine self-administration behavior was similar across the sexes and so they were pooled for analysis. LgA rats took more nicotine than IntA rats did. However, the two groups later showed similar responding for nicotine under progressive ratio, and similar cue- and nicotine-induced reinstatement. Thus, intermittent nicotine use is just as effective as continuous use in producing addiction-relevant behaviors, despite significantly less nicotine exposure. Our findings have implications for

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modeling in rats nicotine-induced changes in brain and behavior at different stages of the addiction process.

3-F-399: The effects of bisphenol S exposure on memory in gonadally intact male and female mice

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Bisphenol A (BPA) is an industrial chemical extensively used in the production of polycarbonate plastics and epoxy resins, resulting in sustained low levels of human environmental exposure. BPA has been a particular focus of concern, due to its endocrine disrupting properties, including effects on metabolic processes, as well as on the central nervous, reproductive and immune systems. Low dose BPA exposure attenuates spatial and non-spatial memory performance, while also reducing the neuroplastic effects of sex steroids in the brain. These effects have prompted replacement of BPA with structurally-related chemicals, such as bisphenol S (BPS). However, whether BPS is actually safer is an open question because its biological effects have not yet been fully explored. In this study, we directly compared the effects of BPA and BPS exposure on spatial memory in mice. Adult male and female CD-1 mice were exposed to BPA or BPS via voluntary, oral administration in a small quantity of peanut butter for 10 days. Both bisphenols were administered at the US Food and Drug Administration "safe daily limit" for human BPA exposure (50ug/kg b.wt./d). Mice were then tested in a home cage object-placement paradigm, followed 24h later by brain tissue and serum collection for neuronal morphological and hormone analyses, respectively. Both BPA and BPS reduced memory performance, in a non sex-specific manner. Thus, the most widely used BPA replacement, BPS, may not be a "safer" alternative than BPA, at least as far as effects on cognitive function are concerned.

3-F-400: Irrational choice via curvilinear value geometry in ventromedial prefrontal cortex

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Why do we make bad choices? A behavioral economist might look for algorithmic or psychological bounds on rational decision-making. However, decision-making can also be bounded by hardware: by constraints on how well our brains can represent the offers in front of us. Fortunately, emerging mathematical tools mean that we can now directly examine how information is represented in neuronal populations. Here, we applied these tools to neuronal recordings from the ventromedial prefrontal cortex (vmPFC, area 14), a part of the prefrontal cortex implicated in economic decision-making. In contrast to what we expected from single-neuron studies, offer values were not represented linearly in the vmPFC population. Instead, value traced a predictable, but curvilinear manifold through neuron-dimensional space. This curvilinear geometry predicted a surprising violation of rational choice theory: a violation of the axiom that terrible offers--offers that will never be chosen--should not affect preferences between better offers. Indeed, we found that monkeys were more likely to confuse two good options when a third, irrelevant offer was worse, compared to when the third offer was better (when the set should have been harder to discriminate, not easier). Past theoretical work showed that linear representations of value could permit neural circuits to generate rational

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economic decisions. However, our results suggest that the neural representation of value is nonlinear. This nonlinearity could contribute to the systematic patterns of irrational choice highlighted in behavioral economics.

3-F-401: Development of a novel model to examine state-dependent dynamic responses to a threat: influence of sex

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Physiological state change recontextualizes environmental stimuli to prioritize immediate needs and recover homeostasis. Threatening stimuli may become differentially influential when energy intake is necessary for survival. During natural conditions such as foraging, animals are presented with stimuli that necessitate behavioral responses such as approach or avoidance. We developed a novel model to examine this behavioral conflict. In our model, adult rats (male and female) are either sated or food deprived (FD) and then placed into an open arena that is baited with food and contains a covered refuge box. Inside the arena, a dynamic predator robot with sensors aimed in range of the food pellets becomes triggered and rapidly approaches the rat once a food area is entered. Animals must weigh threat-engagement against food procurement or exploration. In both sexes, robot presence promotes a significant increase in avoidance behaviour, characterized by flight to the refuge box. Not surprisingly, FD rats consumed more food than sated rats, but interestingly, presence of the robot predator suppressed food intake in FD male rats but not female rats. Consistent with this, males also spent a significantly greater amount of time in the refuge than females in response to the predator. These findings suggest a significant sex-difference in approach/avoidance strategies between sexes, namely that males are more risk-averse in a foraging task involving a dynamic threat.

3-F-402: Brain regions and epigenetic mechanisms involved in second order fear conditioning

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Second order conditioning (SOC) of fear forms when a previously shock-paired conditioned stimulus (CS1) is associated with a new neutral stimulus (CS2).CS2 acquires the same negative valence as CS1, indicated by freezing behaviour in rats. SOC has been shown to engage transcriptional and epigenetic mechanisms in the basolateral amygdala (BLA). However, whether other sensory areas are involved in SOC is not known. Here we conducted cFos and epigenetic marker mapping in rat brains after fear memory retrieval upon CS2 presentation. Odor, context, and tone may be used interchangeably as conditioned stimuli to produce SOC in rats. We first compared cFos activation across multiple brain regions upon presentation of a shock-paired odor CS1, or an odor CS2, CS1 being a tone or context. Following conditioning, shock-paired odor CS1 presentation enhances cFos expression in the anterior BLA, piriform cortex, and dorsal and ventral CA1. Similar patterns of cFos are observed if an odor CS2 has been associated with a context CS1. However, when a tone serves as CS1, odor CS2 enhances cFos expression in the auditory cortex. We then mapped changes in epigenetic markers for histone acetylation (H3Ac, H4ac) and DNA methylation (5MC) following tone CS1 + odor CS2 conditioning. A

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CS1/CS2 unpaired group was used as a control. The conditioned group showed elevated H3Ac and H4Ac expression in the BLA and piriform cortex. Moreover, the elevated H4Ac in the dorsal hippocampus of conditioned group was observed. Our data suggests that primary sensory cortices and the hippocampus are involved in SOC.

3-F-403: Morphine as an interoceptive discriminative stimulus alters morphine reward in female rats

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Interoceptive stimuli elicited by drugs of abuse form associations with exteroceptive cues. Feature positive (FP) and feature negative (FN) occasion setters disambiguate associations of exteroceptive conditioned stimuli and appetitive unconditioned stimuli. Here we investigate whether morphine can act as an occasion setter, and also determine the effect of this learning history on morphine reward. Male and female rats were assigned to FP or FN training, and received daily intermixed morphine or saline injections before each training session. On morphine sessions, FP rats received white noise (WN) presentations that were followed by access to sucrose, but withheld on saline sessions. FN rats learned the reverse contingency. After conditioning, rats underwent place conditioning, and morphine was paired with a distinctive context of a 2-sided chamber. In pairing sessions, rats received alternating morphine or saline injections and access was restricted to the appropriate side. When rats were tested for preference, they had access to both sides of the chamber following no injections. Training with morphine as an occasion setter resolved the ambiguity of reward-predictive exteroceptive cues. In male rats, regardless of learning history, rats spent more time on the morphine-paired side of the chamber. In female rats, however, a history of FP learning increased the rewarding value of morphine compared to FN learning. These data indicate that a history of learning affects the rewarding value of morphine differently in male and female rats.

3-F-404: Investigating the conditioned enhancing properties of a morphine interceptive discriminative stimulus in male and female rats

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Interoceptive sensations elicited by drugs of abuse can form associations with surrounding stimuli in a manner similar to externally perceived (i.e., exteroceptive) cues. A wide range of interoceptive stimuli have been established to guide behaviour in male rats. Here we extend that research to an opioid agonist stimulus, in both males and females. We predicted that when paired with an appetitive outcome, morphine could imbue that drug state with increasing appetitive value. Male and female rats were assigned to a feature positive (FP) or feature negative (FN) group and received daily intermixed morphine or saline sessions. For FP rats, on morphine sessions, each white noise (WN) presentation was followed by access to sucrose; on saline sessions, WN was still presented, but sucrose was withheld. FN rats learned the reverse contingency. After conditioning, rats learned to lever-press for intravenous access to morphine to assess motivation for the interoceptive stimulus. Indeed, morphine can resolve the ambiguity of reward-predictive cues in male and female rats. In

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males, an appetitive learning history with morphine imbued the interoceptive stimulus with conditioned reinforcing properties such that FP males showed greater morphine self-administration compared to FN counterparts. In contrast, there were no differences in morphine self-administration between FP and FN-assigned female rats. These data indicate that the valence of a learning history with an internally-perceived stimulus can alter its subsequent reinforcement value in a sex-dependent manner.

3-F-405: Ketamine reduces fidelity of mental representations in the primate prefrontal cortex

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Ketamine is a N-methyl-D-aspartate receptor (NMDAR) antagonist and in small doses, it produces symptoms of schizophrenia, including impaired mental representations that underlie processes like working memory (WM). Computational models of NMDAR dysfunction point to an increased cortical E/I ratio leading to less stable mental representations. However, it is unclear how synaptic alterations translate into changes in local circuit function that ultimately influence cognition. We administered ketamine to rhesus monkeys during a spatial WM task set in a virtual environment. During task trials, a target was presented at 1 of 9 locations. The target then disappeared during a two second delay epoch, after which the animals were required to navigate to the cued location using a joystick. We recorded neuronal activity using two 96-channel Utah Arrays implanted in LPFC area 8a. We show that unstable sustained activity patterns reduced the sharpness of mental representations which led to WM deficits while sparing perceptual and motor skills. Decreased firing of inhibitory interneurons and increased firing of excitatory neurons resulted in a decrease in neuronal tuning and information encoded by neuronal populations about remembered target locations. These results demonstrate that NMDAR blockage leads to reduced fidelity of mental representations due to unstable network dynamics via cortical inhibition. Results may reflect mechanisms by which WM deficits and perceptual abnormalities arise in individuals with schizophrenia.

3-F-406: Measuring the spatiotemporal scale of prefrontal population codes for visuospatial working memory

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The lateral prefrontal cortex (LPFC) plays a key role in working memory (WM). Electrophysiological studies in monkeys show that LPFC neurons robustly encode visuospatial WM content. However, fMRI studies in humans report weak WM signals in LPFC. We hypothesize that the contradiction arises because the spatial topography of prefrontal population codes for WM is too fine to be effectively resolved by standard fMRI (2x2x2 mm^3, 1-2 s resolution). To test this hypothesis, we analyzed data from microelectrode arrays (Utah array, 4x4 mm^2, 10x10 electrodes spaced 0.4 mm apart) implanted in LPFC areas 8A/46 of

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two macaques performing a spatial WM task. To assess the spatiotemporal scale of population codes, we applied different degrees of spatial (2D Gaussian kernels, 0.2-4.4 mm FWHM) and temporal (1D Gaussian kernels, 2-2048 ms sigma) smoothing to the data and assessed how this affected decoding of WM content. Decoding accuracy is above chance ($p<0.05$, permutation test) for all but the lowest levels (2-8 ms sigma) of temporal smoothing. Furthermore, decoding accuracy improves as a result of increased temporal but not spatial smoothing. The results suggest that coding of remembered stimuli is stable across time for at least a few hundred milliseconds, but not stable across space - channels with similar selectivity do not seem to cluster together. The spatial resolution of standard fMRI may be insufficient to robustly detect prefrontal population codes for WM. High-field fMRI, with increased spatial resolution, may be able to bridge the gap between electrophysiological and fMRI studies.

3-F-407: Impact of physical activity at the onset of the COVID-19 pandemic on mood and mental health over time

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Physical activity and healthy eating are vital elements for establishing metabolic and mental health. We recently showed that unhealthy snacking is a strategy used to cope with stress during the coronavirus disease 2019 (COVID-19) pandemic. Here, we implemented a longitudinal survey with 319 participants in May (Phase P1) and October 2020 (P2) to assess whether physical activity can improve mood and mental health outcomes over time. There was a decrease in leisure-time physical activity, but not on-the-job activity, from P1 to P2. Lower leisure-time physical activity in P1 was associated with appraisals of uncontrollability in P2. These appraisals predicted worsened mood, and increased feelings of depression, anxiety, or stress in P2. We then conducted mediation models to determine if uncontrollability underlies the relationship between P1 leisure-time physical activity and subsequent mood and mental health outcomes in P2. Interestingly, we found that when situations were appraised as uncontrollable in P2, the level of leisure-time physical activity in P1 was predictive of worsened mood and mental health outcomes in P2. In aggregate, we surmised that physical activity at the onset of the pandemic indirectly predicted mood and mental health outcomes 4 months later. This suggests that physical activity may protect against the widespread stress and lifestyle changes inflicted by COVID-19.

3-F-408: The smart vivarium v1.0: implementation and validation

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The set of behavioral strategies we develop to manage stress stems from social interactions. Similarly, chronic stress models in rich environments in mice models, simplify the analysis of environmental and social factors using an automated assessment and tracking system. In a large group, mice are so influenced by pressures from other members of the group that over time, the evolutionary structure is formed by the social hierarchy in the group. For example, in this evolutionary structure, in rich and complex environments, group members interact with each other, sometimes play, and sometimes fight with each other to prove their dominance to the group. The behavioral ability that each mouse exhibits during daily life to

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control stress determines its status in the colony. The goal of this project is to develop an automated behavioral platform using machine-based units and a radio-frequency identification system (RFID) to evaluate the behaviors resulting from chronic variable stress (CVS) in male and female mice in groups ethically. To achieve our goals, we have developed two smart vivariums (1m x1m) equipped with high-quality cameras including various components such as beddings, enrichments, food, nesting material, games and toys, bridges, and ropes for each group of male and female. We control the behavioral characteristics of different groups up to a maximum of 10 people for 6 weeks by these smart vivariums at the same time for both mice groups and finally archive them in cloud data storage. To that end, we created an extensive library of several thousand images of different mice to automatically detect these individual or group behavioral characteristics by tracking them through a hybrid machine system consisting of DeepLabCut and YOLO with an RFID system.

3-F-409: Antagonists of noradrenergic and corticotrophin-releasing factor receptors block enhancement of memory consolidation by heroin withdrawal and conditioned heroin withdrawal

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AIM: Opioid withdrawal can be associated to environmental cues through classical conditioning to produce conditioned withdrawal. Recent preclinical evidence suggests that exposure to these cues can have profound cognitive effects and can play a role in the addiction by enhancing memory consolidation. To further understand the neurobiological mechanism by which cues influence memory, this study investigated the roles of two stress neuromodulators: noradrenaline and corticotrophin-releasing factor. METHODS: In Experiment 1, 0-3 mg/kg naloxone, 0.1 - 0.6 mg/kg lofexidine (alpha-2 adrenergic agonist) and 10 - 20 mg/kg antalarmin (CRF1 antagonist) were co-administered shortly after training on the object recognition task to heroin-dependent rats (via subcutaneous osmotic mini-pumps; 3.5 mg/kg/day). In Experiment 2, heroin-dependent rats were confined for 2 hours in a context (CS) following naloxone injections and in another context (CS-) following vehicle injections. The effects of immediate post-training exposure to the CS (or CS-) and co-administration of lofexidine and antalarmin were tested 7 days after removal pumps. RESULTS: It was found both lofexidine and antalarmin dose-dependently blocked the enhancement of object memory consolidation by post-training naloxone precipitated withdrawal and by conditioned withdrawal. CONCLUSIONS: These experiments suggest that pharmacological and psychological withdrawal have significant effects on memory storage by activating noradrenergic and CRF stress systems.

G - Novel Methods and Technology Development

3-G-410: Exploration of the red blood cell biomechanics with digital holographic microscopy: Towards a methodology to identify cellular phenotypes related to major psychiatric disorders

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Major psychiatric diseases (MPDs), including schizophrenia, are diagnosed very late, due to the lack of effective biomarkers. Post-mortem analyzes show that the lipid composition of neuronal membranes differs in people with schizophrenia. This difference is also reflected in several types of cells, including red blood cells (RBCs). RBCs are known to exhibit spectacular biomechanical properties (BPs) resulting in unique deformability capacity and spontaneous membrane vibrations at the nanoscale . It has been reported that the lipid composition of the RBC membranes affects these BPs. An accurate biomechanical characterization of RBCs could thus reveal MPD-related phenotypes. Quantitative Phase Digital Holography Microscopy (QP-DHM), providing images with a nonmetric axial sensitivity, represents a highly relevant technique to quantitatively study the RBC biomechanics. As a first step to identify MPD-related RBC phenotypes, we have started to develop a methodology based on QP-DHM to characterize RBC biomechanics. Studies are conducted in different conditions known to specifically impact RBC BPs. Concretely membrane vibrations and RBC deformations are monitored in environments controlled for temperature, ph, O2 and CO2 partial pressures. We are also going to start a biomechanical study of RBCs obtained from mice, having benefited from a strict diet allowing a control of their membrane lipid composition. Then, aiming at identifying MPD-related RBC phenotypes, we will apply this methodology on our clinical data set, composed or RBC samples collected from patients suffering for MPDs.

3-G-411: At-home cognitive training during the COVID-19 Pandemic? Validation, utility and lessons for future research

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Introduction: The COVID-19 pandemic has created a shift in the use of at-home spaces for work, play and research. In the present study we sought to determine if NeuroTrackerX, an anaglyph, at-home version of the three-dimensional multiple object tracking (3D-MOT) software NeuroTracker, produced similar results to the laboratory version that uses active 3D technology. Methods: 20 cognitively healthy adults (10 female, mean age = 68.3 years, SD = 6.75) were recruited for participation as the at-home training group. 20 participants, above 50 years old, who had previously completed at least 8 session of in-lab 3D-MOT, were randomly selected to serve as the in-lab control group. At-home participants were loaned the necessary equipment (e.g. 3D-glasses, computer equipment), and engaged in 10 training sessions over five weeks (2x per week). Results: No demographic differences were observed between the two groups (age, sex, MMSE score). The in-lab control group performed better on the task at session one ($p < 0.05$), however no differences in session scores ($p > 0.05$), or learning rates ($p > 0.05$) were observed between groups over the remaining sessions. Participants in both groups showed significant improvements in task performance across the training sessions ($p < 0.001$). Conclusions: These results indicate that NeurotrackerX provides a promising in-home option to use for cognitive training in cognitively healthy adults. Future studies are needed to determine if these benefits can also be observed in cognitively-challenged groups who may benefit from this form of cognitive training.

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3-G-412: Improved methodologies for genetic conversion of human fibroblasts to neurons

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Genetic cell fate manipulation can be used to convert one cell type to another, which facilitates the production of personalized and customized human neurons for basic science applications and disease modeling. Genetic conversions often start with accessible cell types like fibroblasts, which are converted to neurons using multiple lentivirus vectors that encode neurogenic genes, such as Ascl1 and Ngn2; furthermore, for doxycycline (dox) inducibility, another vector is used to deliver a dox-dependent transcriptional regulator (e.g. rtTA or TetR). Such direct cell fate conversion approaches have the advantage of retaining some epigenetic marks, but somatic cells like fibroblasts often grow slowly, and the use of multiple viral vectors decreases conversion efficiencies. To address these limitations, we tested a range of media formulations and found that supplementing serum-based fibroblast media with basic fibroblast growth factor improved growth by 3-fold. We also found that co-expression of Ascl1 and Ngn2 from a single lentivirus vector improved neuronal conversion by approximately 45% compared to the delivery of Ascl1 and Ngn2 on separate vectors. These improvements increase both neuronal conversion efficiency and potential neuronal yield of this fibroblast-to-neuron conversion platform. We are currently developing a self-inactivating "all-in-one" lentivirus, which will express dox-inducible Ascl1-P2A-Ngn2 along with TetR and a selectable marker to isolate pure neuronal populations for studies of human neurobiology and to model disorders of the brain.

3-G-413: Next generation tools for imaging in the cortex and spinal cord

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State-of-the-art imaging tools rely on a restrained preparation, limiting natural behavior while measuring cellular activity via fluorescence (FL). Recently, advances in wearable microscopy expanded the range of accessible behaviors by allowing imaging of freely behaving animals. However, wearable microscopes to this day are primarily used for brain imaging and have not been adopted for imaging other parts of the body, for example the spinal cord. Furthermore, unfavorable attributes of FL indicators constrain the extent of imaging experiments, including photobleaching, autofluorescence and excitation light scattering noise especially in the parts of the body like the spinal cord due to myelination. All 3 of these issues can be eliminated while offering an increase in the imaging depth by using bioluminescence (BL) instead of the FL. Here we demonstrate our ability of imaging BL calcium indicators through the cranial window in mice as fast as 5 frames per second using redesigned open-source miniscopes. Furthermore, we present an expansion of the miniscope use towards neurovascular imaging in the spinal cord. Spinal neurovascular imaging is accomplished by integrating a custom vertebral implant with miniscope hardware that ensures mechanical stability over time. Such implants allow interchangeable imaging of the brain or spinal cord in free or restrained animals. Altogether, our work expands the

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imaging toolbox towards better imaging quality via BL indicators and the ability to image across multiple sites throughout the nervous system using wearable miniature microscopes.

3-G-414: Characterizing the expression, localization, and native targets of SUMOylation in the mouse central nervous system

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SUMOylation is an evolutionarily conserved and essential post translational modification by which Small Ubiquitin Like Modifiers, or SUMO proteins, are covalently bound to substrates in a highly dynamic and readily reversible manner. This process allows for tight spatiotemporal regulation over a wide variety of protein functions. Of the three SUMO paralogs (SUMO1 - SUMO3) shared between humans and mice, Sumo1 and Sumo2 share around 50% homology, whereas mature Sumo2 and Sumo3 share 95% homology. Interestingly Sumo2 is the only essential SUMO protein playing particularly important roles in development of the central nervous system. Studying the roles for SUMOylation in vivo remains challenging as limited tools are available to identify, compare, and contrast SUMO proteins and their targets. We generated a novel mouse model to study SUMOylation in the central nervous system by knocking in a hemagglutinin (HA) tag into the endogenous Sumo2 locus. Using this mouse line, as well as a previously established HA-Sumo1 knock-in mouse line, we perform immunofluorescent characterization of differential SUMOylation in various tissues including the central and peripheral nervous system. Moreover, we performed immunoprecipitation coupled with mass spectrometry to compare and contrast the expression, localization, and conjugation of Sumo2 in the mouse brain identifying unique and overlapping targets compared to Sumo1. This model will serve as a valuable tool to study the cellular and biochemical roles of SUMOylation for neuronal function. Future studies will focus on elucidating the roles for SUMO regulation on neuronal function by characterizing the consequences of genetically inhibiting SUMOylation on target substrates of interest.

3-G-415: Are podcasts effective for knowledge dissemination to neuroscientists? Case study: AMiNDR podcast (a month in neurodegenerative disease research)

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Researchers are expected to manage various responsibilities whilst staying up-to date with developments in their field. This is an arduous and time-consuming task. In Alzheimer's disease research alone, an average of 200 research articles are published every week. Last year we presented our podcast, AMiNDR, as a means of easing the burden on researchers. We offer an accessible audio format channel, sorting research into distinct categories and summarizing its contents. Each episode corresponds to a category or subtheme of research, complete with a bibliography of papers covered. In the year since its launch in June 2020, AMiNDR has published over 160 episodes with accompanying bibliographies. While the podcast has received positive feedback from researchers worldwide, we wonder if it is an effective way of disseminating knowledge and if it is achieving its goal of saving scientists

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time. To assess the podcast's reach, we tracked followers' growth and engagement across social media platforms and compared AMiNDR's performance with other prominent science communication podcasts with a similar target audience. We also measured the engagement with our podcast and website using Podcast Analytics and Google Analytics. respectively. We supplemented this with a survey to discern listeners' satisfaction with the service, followed-up with optional interviews for feedback. We present the results of this assessment with a list of recommendations for digital knowledge dissemination tools like the AMiNDR podcast. This will help further refine science communication initiatives in Neuroscience.

3-G-416: A toolbox for the optogenetic control of cAMP in vivo

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Recent optogenetic technologies have demonstrated not only light-dependent control of neuronal activity but also the regulation of target molecules by light, suggesting their potential applications to study cellular functions at the molecular level in the brain. Here, we introduce our optogenetic approaches for the non-invasive manipulation of intracellular cAMP processes with light in target neurons of the brain. cAMP is a ubiquitous secondary messenger for intracellular signalling pathways, mediating sensory transduction and neuromodulation. However, cAMP dynamics and related spatiotemporal functions remain elusive in the brain due to limitations of spatiotemporal specificity of pharmacological and genetic approaches to acutely perturb cAMP function. We have optimized and further established genetically encoded light-sensitive cAMP metabolic enzymes to enhance or suppress cAMP levels in living neurons. By expressing the light-sensitive cAMP metabolic enzymes with cAMP fluorescence indicators, we successfully monitored and manipulated cAMP levels of living hippocampal pyramidal neurons in murine hippocampal brain slices with two-photon laser microscopy, validating our optogenetic approaches in the target hippocampal neurons. Furthermore, we incorporated these optogenetic techniques directly in the target hippocampal neurons of freely behaving mice with brain-implanted fiber optic LED devices for light-dependent manipulation of cAMP in the intact brain. We will discuss in vivo optogenetic approaches in combination with murine hippocampus-dependent behavioural tests.

3-G-417: Developing selective fluorophore-tagged activity-based probes for live-cell imaging of active monoamine oxidase

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The neurobiology of depression can increase the risk of developing Alzheimer disease (AD) in later life. The depression-related enzyme monoamine oxidase (MAO) has been implicated in the earliest lesions in the progression of AD. The two isoforms of MAO, e.g. MAO-A and MAO-B, catalyze the degradation of monoaminergic neurotransmitters (e.g. serotonin, dopamine, and noradrenaline) and MAO-mediated neurocytotoxicity may involve hydrogen peroxide (a reaction byproduct). MAO protein expression and catalytic activity often do not correlate and an unrecognized pool of inactive MAO could bias results and give rise to misleading conclusions. Perhaps this explains why MAO inhibition has been only modestly

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successful in clinical AD populations. It is impossible to differentiate active from inactive MAO protein in cells and tissues. Activity-based probes (ABPs) are probes designed to attach to the catalytic sites of active enzymes. Exploring this concept, our team has synthesized three fluorescent ABPs and using recombinant MAO-A and MAO-B proteins, endogenous (LnCAP cells) and overexpressed (N2a cells) MAO proteins, and confocal microscopy, we demonstrate that these probes bind irreversibly and selectively to MAO-A. This will benefit future live-cell imaging studies. ABPs, especially highly selective candidates, will give us a better understanding of the function of MAO-A and MAO-B in health and could help define a role for MAO in pathology and provide for a stage-specific therapeutic intervention strategy with benefit for clinical depression as well as AD.

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