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2019 Poster Abstracts

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Poster session 1: May 23, 2019

A - Development

1-A-1 *Polygenic scores based on prefrontal and striatal dopamine transporter gene network interact with early adversity score to predict fat intake and impulsivity in children*

Barbara Barth[1], Zihan Wang[1], Irina Pokhvisneva[1], Danusa Arcego[1], Euclides Mendonca Filho[2], Michael Meaney[1], Patricia Silveira[1]

[1]McGill University, [2]UFRGS

The mechanisms involved in the co-morbidity between metabolic and psychiatric disorders (e.g. obesity and ADHD) are poorly understood, and variations in the responsivity to environmental adversity could be involved. Dopaminergic neurons constitute a system underlying the brain response to both adverse and protective environmental conditions. Here we analyzed the interaction between genetic scores associated with the dopamine transporter gene network (DAT1) and environmental adversity on fat intake and impulsivity levels in children (MAVAN Project). Scores based on genes co-expressed with the DAT1 on the prefrontal cortex and striatum were created using the effect size of the association between the individual SNP from those genes and gene expression (GTEx). Macronutrient intake (Food Frequency Questionnaire) and reflection impulsivity (Information Sampling Task, CANTAB) were used as outcomes. There is a significant interaction between PFC-DAT1 score and adversity on impulsivity at 72 months (β=-21.28; $p<0.05$) and between the Striatum DAT1 score and adversity on % intake of saturated fatty acids at 48 months (β=-60.17; $p<0.05$). Interactions showed evidence of differential susceptibility according to Roisman et al (2012), suggesting that the same group at risk under poorer environments has better outcomes under positive conditions. The genetic scores are brain region-specific (PFC-DAT1 score does not predict impulsivity and Striatum DAT1 score does not predict fat intake). These findings may have important implications for obesity and psychopathology prevention.

1-A-2 *Translational approach to investigate the role of leptin receptors on the association between early life adversity and eating behavior*

Randriely Merscher Sobreira de Lima[1], Ana Paula Santana de Vasconcellos Bittencourt[2], Danusa Mar Arcego[3], Euclides José de Mendonca Filho[1], Sachin Patel[4], Carla Dalmaz[1], Michael Meaney[3], Patricia Pelufo Silveira[3]

[1]Universidade Federal do Rio Grande do Sul, [2]Univeridade Federal do Espírito Santo, [3]McGill University, [4]Ludmer Centre for Neuroinformatics and Mental Health

Exposure to early adversity is associated with eating behavior and body weight regulation, but the mechanisms are yet to be investigated. We propose a translational approach to study interactions

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between early life adversity and eating associated with the leptin receptor gene (LepR). We submitted Wistar rats to Maternal Separation (MS; from 2nd to 14th postnatal days (PND); 3 h/day) or a Maternal Deprivation (two 24-hour periods on 9th and 11st PND). At 60th PND, consumption of standard chow was assessed and expression of LepR was analyzed in the hypothalamus by RT-PCR. Based on the animal data, we created an expression-based polygenic risk score (ePRS) reflecting variations in the function of the LepR gene network in different brain regions and investigated its interaction with postnatal adversity on satiety (Child Eating Behaviour Questionnaire) in 4y.o. children (MAVAN cohort). In rats, MD decreases chow intake in adulthood (P=0,001), and MS showed a trend towards increase in the hypothalamic expression of LepR (P=0.08). In children, there is an interaction between adversity and prefrontal-based LepR-ePRS and a trend to LepR-ePRS on the amygdala on satiety responsiveness (β =-99.29; P=0.01 and β=50.97; P=0.05 respectively), but no effects were found using the hypothalamus-based LepR-ePRS (β= -72.45; P=0.13). These results indicate that the impact of postnatal adversity on eating can be moderated by gene networks associated with leptin signaling.

1-A-3 *Elucidating the role of the imprinted gene network in retinal regeneration*

Luke David[1], Yacine Touahri[1], Carol Schuurmans[1]

[1]Sunnybrook Research Institute

In response to injury, mammalian Müller glia (MG) fail to proliferate and de-differentiate into progenitor cells that can regenerate lost cells. Instead, mammalian MG activate a cytotoxic process known as reactive gliosis. Previously, our lab identified an imprinted gene, Zac1, that is an essential negative regulator of MG cell proliferation. Consequently, we aim to elucidate the role of other imprinted genes that are co-regulated with Zac1, all of which are part of an Imprinted Gene Network (IGN). Our hypothesis is that additional components of the IGN also participate in the mammalian MG regenerative response. Accordingly, we investigated the expression profiles of IGN genes in the retina. Subsequently, we designed antisense RNA probes to analyse the spatial distribution of IGN transcripts in the retina, revealing that similar to Zac1, some of these genes are expressed in MG. In addition, we quantitated the expression of IGN genes in the context of retinal degeneration by RTqPCR. Our data revealed that IGN gene expression is mis-regulated in response to methylnitrourea (MNU)-induced retinal injury. These data revealed that components of the IGN are expressed by MG and that these genes are responsive to injury, suggesting a potential role in controlling retinal regeneration. Next steps will involve the manipulation of the expression of these genes in MG to assess their functional role in the regenerative response. Insights gained in characterizing new molecular factors that control mammalian retinal repair will undoubtedly bring us a step closer to combatting eye diseases.

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1-A-4 *Dopamine-related polygenic scores (D2, D4, DAT1) and exposure to postnatal adversity and sucking habits in infants*

Kelly Guedes de Oliveira Scudine[1], Zihan Wang[2], Irina Pokhvisneva[2], Paula Midori Castelo[3], Michael Meaney[2], Patricia Pelufo Silveira[2]

[1]Piracicaba Dental School-UNICAMP, [2]McGill University, [3]Universidade Federal de São Paulo (UNIFESP)

Considering that dopamine is the primary neurotransmitter involved in reward expectation and goal-directed behavior, genomic polymorphisms reflecting the gene network comprising genes of the dopaminergic system can be valuable to better understand predispositions to reward-based behaviors like sucking habit (pacifier and thumb sucking). Thus, the objective of this study was to investigate if polygenic scores reflecting the gene network of dopamine receptors (ePRS-D2, ePRS-D4) and dopamine transporter (ePRS-DAT1) in striatum and prefrontal cortex predict the presence of sucking habits in infants, in the presence of postnatal adversity. The sample was comprised of 146 infants from Montreal (Quebec) and Hamilton (Ontario), Canada, recruited from an established birth cohort called MAVAN (Maternal Adversity, Vulnerability and Neurodevelopment). We observed a significant interaction in: 1) ePRS-DAT1.PFC x A ($p < 0.01$) at 3 months; 2) ePRS-D2.STR X A ($p < 0.01$) at 6 months; 3) ePRS_DRD4.STR X A ($p < 0.01$) at 6 months, which the high ePRS group demonstrated higher prevalence of sucking habit with increased A exposure; 4) ePRS-DRD2.PFC x A ($p < 0.01$) at the 12 months, with high ePRS group demonstrating lower prevalence of sucking habit in more adverse environments. No significant interactions were observed in the low ePRS group. These findings reveal the impact of genetics and the environment on the presence of sucking habits during the first year of life, which D2, D4, DAT1 seem to be an important player in modulating this behavior.

1-A-5 *mTOR inhibition restricted to a postnatal sensitive period rescues the deficits in GABAergic PV cell connectivity and social behavior caused by loss of Tsc1*

Mayukh Choudhury[1], Clara Amegandjin[1], Vidya Jadhav[1], Josianne Carriço[2], Ariane Quintal[1], Martin Berryer[1], Bidisha Chattopadhyaya[2], Graziella Di Cristo[1]

[1]Université de Montréal, [2]CHU Sainte-Justine Research Center/Université de Montréal

Properly functional cortical circuits depend on the correct development of inhibitory interneurons. In particular, the axonal arborisation and synapse density of parvalbumin (PV)-positive GABAergic interneurons undergo striking changes in the young brain. The Mechanistic Target Of Rapamycin Complex 1 (mTORC1) pathway, which is regulated by Tuberous Sclerosis (TSC) 1 and 2 proteins, has been implicated in controlling several aspects of neuronal development. How and whether

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mTORC1 signaling affects PV cell development is unknown. Here, we showed that Tsc1 knockout (KO) in single PV interneurons in cortical organotypic cultures caused a premature increase in terminal axonal branching and bouton density formed by mutant PV cells, followed by a striking loss of perisomatic innervation after the 4th postnatal week. To investigate the role of mTORC1 in PV cells in vivo, we bred Tsc1lox with Nkx2.1-Cre and PV-Cre mice to knockout Tsc1 before and after birth, respectively. Both conditional KO mice showed mTORC1 hyperactivation in PV cells. Consistently to what observed following Tsc1 KO in single PV cells, PV cell perisomatic innervations were increased at P18, but decreased at P45 in Nkx2.1-Cre;Tsc1lox/lox mice compared to controls. Further, both conditional KO mice showed alterations in social behavior. Finally, treatment with the mTOR inhibitor Rapamycin restricted to the third postnatal week was sufficient to rescue deficits in PV cell innervation in PV cell innervation in organotypic cultures and social behavior in vivo in conditional heterozygous but not homozygous mice.

1-A-6 *Modulation of gut microbiota leads to changes in intestinal permeability: How commensal bacteria could affect the gut-brain-axis*

Abby McDonell[1], Josue Jaramillo Polanco[1], Alan Lomax[1]

[1]Queen's University

A growing emphasis has been placed on the importance of the gut-brain-axis (GBA) and its modulation by the gut microbiota. Studies from our lab suggest that a gut bacterial community derived from a healthy donor (microbial ecosystem therapeutics; MET-1) modulates afferent signalling in the GBA. However, the mechanisms that allow microbes in the gut lumen to signal across the mucosa and influence the nervous system are unknown. We hypothesized that the disruption of the microbiota with antibiotics, or mimicking the microbiota in vitro with MET-1 would alter the intestinal barrier. In vivo permeability assays consisted of orally administering antibiotic-treated or control mice a fluorescent dextran and measuring its concentration within the serum. In vitro studies in Ussing Chambers examined changes in FITC dextran flux from the lumen to the serosa of the colon of mice receiving the antibiotic treatment or MET-1 (1:1000) in vitro. Colonic permeability to FITC dextran was significantly increased in vivo within the antibiotic-treated group compared to controls. However, no change in colonic FITC dextran permeability was reported between the groups in vitro. Conversely, colons exposed to MET-1 in vitro displayed an increase in dextran permeability compared to controls. These results indicate that the modulation of host microbiota leads to changes in mucosal permeability, which may facilitate the access of microbial metabolites to the nervous system.

1-A-7 *Developmental access to the principal spinothalamic neuron population of the lumbar spinal cord*

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Farin B. Bourojeni[1], Artur Kania[2]

[1]McGill University, [2]Institut de Recherche Clinique de Montreal (IRCM)

Nociception relies on the appropriate integration of both somatosensory and emotive inputs in the brain. Somatosensation is established as a multi-level organisation. It relies on the activation of peripheral sensory neurons that synapse onto second-order spinal neurons that project to various brain targets, including the lateral thalamus. These third-order thalamic neurons then relay this sensory input onto the cortex for the integration of an appropriate reactionary motor response. Although, the spinothalamic (ST) neurons are central to this organisation, little is known about their developmental organisation and relative contribution to nociception. We demonstrate that ST neurons arise from multiple developmental lineages and migrate to populate distinct domains of the spinal cord. In particular, at the hindlimb level, ST neurons are predominantly derived from the V3 cardinal group marked by the expression of the Sim1 transcription factor, as well as the dI5 group expressing Lmx1b. While Lmx1b ST neurons are located in the superficial dorsal horn (DH) and lateral spinal nucleus, Sim1 ST neurons give rise to the deep DH ST population. The central endings of primary nociceptors form appositions on Lmx1b ST neurons. In contrast, Sim1 ST neurons coincide with proprioceptive inputs. Furthermore, Lmx1b and Sim1 ST neurons display regional innervation biases in the thalamus. Collectively, we propose that the developmental origin of spinothalamic neurons defines their functional role in the relay of nociceptive, tactile and proprioceptive inputs for thalamic integration.

1-A-8 *Neuronal primary cilium, a remote control of axonal development*

Jiami Guo[1], James Otis[2], Sarah Suciu[3], Sandii Constable[3], Lei Xing[4], Tamara Caspary[3], Eva Anton[4]

[1]University of Calgary, [2]Medical University of South Carolina, [3]Emory University, [4]University of North Carolina at Chapel Hill

Appropriate axonal growth and connectivity are essential for functional wiring of the brain. Joubert Syndrome Related disorders (JSRD), a group of ciliopathies in which mutations disrupt primary cilia function, are characterized by axonal tract malformations. However, little is known about how cilia-driven signaling regulates axonal growth and connectivity. We demonstrate that the deletion of JSRD gene Arl13b in projection neurons leads to axonal defects in SCP (superior cerebellar peduncle), CST (corticospinal tract), and CC (corpus callosum) axonal tracts. Arl13b deletion disrupts the function of its downstream effector Inpp5e and deregulates ciliary-PI3K/AKT signaling necessary for axonal development. Chemogenetic activation of ciliary-GPCR signaling and cilia-specific optogenetic activation of downstream second messenger cascades (PI3K, AKT, AC3) induce rapid changes in axonal dynamics. These data suggest that ciliary signaling mechanisms

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act to modulate the formation of axonal tracts and connectivity in the developing brain and that impaired primary cilia signaling underlies axonal tract defects in JSRD.

1-A-9 *The multipolar-to-bipolar transition of developing mammalian cortical neurons is regulated by the Glo1-methylglyoxal pathway*

Lamees Mohammad[1], Guang Yang[1]

[1]University of Calgary

In the developing mammalian cortex, newborn neurons undergo substantial morphological and metabolic changes during maturation. Newborn neurons initially exhibit a multipolar shape with several short processes, and then gradually adopt a bipolar morphology by retracting most short neurites and extending two thick processes, which relies on glycolysis to provide energy for rapid axon growth. A successful transition to the bipolar shape is critical for neurons to mature and migrate into the cortical plate, where they integrate into complex neural circuits. However, how the metabolic program regulates the multipolar-to-bipolar transition is still not well understood. Here, we show that glyoxalase 1 (Glo1), a glycolysis-related enzyme, plays an important role in this transition by metabolizing and balancing the levels of methylglyoxal, an intermediate metabolite of glycolysis. Knockdown of Glo1 using short-hairpin RNA or inhibiting the enzymatic activity of Glo1 in cultured mouse cortical neurons significantly impairs their transition from the multipolar to bipolar shape. This morphological perturbation is recapitulated when neurons are treated with excessive methylglyoxal. Furthermore, Glo1 knockdown in the developing cortex similarly causes morphological transition defects of newborn neurons, impeding their migration into the cortical plate. Our results suggest a novel link between glycolytic metabolism and neuronal maturation.

1-A-10 *Neurog2 and Ascl1 function as a neurogenesis switch*

Sisu Han[1], Imrul Faisal[2], Grey Wilkinson[3], Satoshi Okawa[4], Lata Adnani[3], Matthew Brooks[5], Vladimir Espinosa Angarica[4], Dawn Zinyk[2], Saiqun Li[3], Rajiv Dixit[2], Yaroslav Ilnytskyy[6], Eko Raharjo[3], Jung-Woong Kim[5], Wei Wu[3], Faizan Malik[3], Waleed Rahmani[3], Diog

[1]University of Toronto, [2]Sunnybrook Research Institute, [3]University of Calgary, [4]University of Luxembourg, [5]National Institutes of Health, [6]Lethbridge University, [7]Instituto Gulbenkian de Ciência

In tissues with a temporal mode of cell fate specification, some stem cells differentiate while others are retained for later differentiation events. To examine stem cell retention in neural lineages, we stratified the neural stem cell (NSC) pool in the embryonic neocortex into four populations based

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on proneural gene expression (negative, Neurog2+, Ascl1+, double+). Double+ NSCs display the lowest proliferative capacity, with a prolonged S-phase, slower cycling times, and elevated expression of negative cell cycle regulators. Double+ NSCs are uncommitted, whereas single+ NSCs are lineage biased. Based on open chromatin and gene expression, double+ NSCs lie at the top of a lineage hierarchy, and have a complex transcriptional regulatory network permissive for Neurog2 or Ascl1 lineage conversion. Mechanistically, Neurog2 and Ascl1, which specify competing neural cell fates, maintain uncommitted NSCs by antagonizing each other's functions. We thus implicate proneural gene co-expression and multi-lineage priming in the maintenance of embryonic NSCs.

1-A-11 *Molecular and cellular changes that define Müller glial cell dedifferentiation in the regenerating retina*

Jeffrey Stulberg[1], Cassandra D'Amata[2], Alyssa Molinaro[1], Bret Pearson[3], Vince Tropepe[1]

[1]University of Toronto, [2]The Hospital for Sick Children, [3]University of Toronto and The Hospital for Sick Children (SickKids)

The mature zebrafish retina contains a population of cells known as Müller glia (MG), a relatively quiescent radial glial cell with stem cell properties capable of regenerating retinal cells in response to acute lesions. Recently, MG have been shown to undergo interkinetic nuclear migration (IKNM) during regeneration, though the gene networks that regulate the initiation of MG IKNM have yet to be identified. Furthermore, evidence has shown that not all MG cells respond to retinal injury, and those that do are activated in temporal cohorts, suggesting that the MG population itself may be heterogeneous. We aimed to characterize MG IKNM and investigate the role of Notch signalling as it has previously been implicated in maintaining MG cell cycle quiescence. In addition, we performed single-cell RNA-sequencing on MG cells before and after a photoreceptor lesion to obtain an unbiased sampling of the gene networks that are involved in the early MG regenerative response. Preliminary data indicates that Notch is highly dynamic and is downregulated prior to the initiation of MG nuclear migration but is re-established before MG cells re-enter the cell cycle. Clustering of single-cell gene expression provides preliminary evidence for distinct subgroups of MG. We plan to identify putative interactors and downstream mediators of the Notch signalling cascade in our scRNA-seq dataset. We anticipate that these experiments will elucidate a novel role for Notch in MG regeneration and will resolve the degree of MG heterogeneity and identify molecular signatures that promote MG regeneration.

1-A-12 *Epigenetic regulation of postembryonic neurogenic plasticity by the histone methyltransferase Ehmt2*

Francesca Meda[1], Steven Deimling[1], Vincent Tropepe[1]

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[1]University of Toronto

Epigenetic regulation plays an important role in neurogenesis, controlling both neural stem cell self-renewal and differentiation potential. The histone methyltransferase Ehmt2 (also known as G9a) has been recently implicated in the processes of neuronal development and plasticity, as well as in learning, memory and response to environmental stimuli in different organisms. However, the role of Ehmt2 in neurogenesis remains unclear. Ehmt2 catalyses the addition of two methyl groups onto lysine 9 of histone 3 (H3K9me2), promoting repression of transcription. To decipher the role of Ehmt2 during neurogenesis, we generated a zebrafish Ehmt2 mutant line (Ehmt2Δ4/Δ4) through CRISPR/Cas9 gene editing. Ehmt2Δ4/Δ4 fish are viable and fertile and, as expected, display reduced H3K9me2 levels in the brain. Beyond Ehmt2's intrinsic role in brain development, the Ehmt2Δ4/Δ4 mutant enabled us to test whether Ehmt2 is involved in tuning the neurogenetic response to sensorimotor experience. Indeed, a leading hypothesis posits that external stimuli are "memorized" by the growing brain in the form of epigenetic modifications. Preliminary results suggest that postembryonic neurogenesis in Ehmt2Δ4/Δ4 fish is differentially affected by the same sensorimotor stimulus compared to WT animals. As a whole, this newly generated Ehmt2Δ4/Δ4 mutant line will help to reveal the role of Ehmt2-mediated epigenetic regulation of neurogenesis in response to sensorimotor experience.

1-A-13 *The importance of dorsal root ganglia in mediating movement-dependent forebrain neurogenesis in zebrafish larvae*

Zachary Hall[1], Vince Tropepe[1]

[1]University of Toronto

During postembryonic development, the brain exhibits substantial experience-dependent neuroplasticity, in which sensory experience guides normal brain growth. Traditionally, experience-dependent neuroplasticity is thought to occur primarily via structural and functional changes in pre-existing neurons. Whether neurogenesis also mediates the effects of experience on early brain growth is unclear. Here, we characterized the importance of motor experience on postembryonic neurogenesis in larval zebrafish. We found that swimming is critical to maintain an expanded pool of forebrain neural precursors by promoting progenitor self-renewal over the production of neurons. Physical cues associated with swimming (tail movement) increase forebrain neurogenesis and these cues appear to be conveyed, at least in part, by dorsal root ganglia (DRG) in the zebrafish body: DRG-deficient larvae exhibit attenuated neurogenic responses to changes in swimming and targeted photoactivation of DRG in immobilized larvae expands the pallial pool of proliferative cells. Our results demonstrate the importance of movement in neurogenic brain growth and provide a fundamental sensorimotor association that may couple early motor and brain development.

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1-A-14 *Role of astrocytes in the control of postnatal brain angiogenesis*

Moises Freitas-Andrade[1], Peter Van Dyken[2], Xavier Toussay[1], Baptiste Lacoste[1]

[1]The Ottawa Hospital Research Institute, [2]University of Ottawa

After birth, cerebrovascular networks rapidly expand and closely interact with astrocytes. However, our fundamental understanding of this glio-vascular interplay during postnatal brain development is limited. Using mice in which the Green Fluorescent Protein is expressed under the control of the astrocyte-specific Aldh1L1 promoter, coupled with endothelial and proliferation markers, we show a strong correlation between astrocyte and endothelial cell (EC) proliferation at postnatal days 0 (P0), P4, P7 and P14. In both astrocytes and ECs, proliferation peaks at P4 and declines by P7, reaching low levels by P14. An assessment of astrocyte development showed that past P7, astrocytes disperse across the brain. By P14, astrocyte processes begin to physically interact with blood vessels. By P21, the neurovascular unit is fully formed, and protoplasmic astrocytes associated with major blood vessels express high levels of Glial Fibrillary Astrocytic Protein. To test whether astrocytes around blood vessels are required for proper angiogenesis, we are now using mice expressing an inducible Cre recombinase under the control of Aldh1L1 promoter, in order to drive conditional removal of the Orc3 allele flanked by loxP sites. The Orc3 gene encodes a core subunit of the origin recognition complex (ORC) essential for DNA replication and cell proliferation. This strategy will provide an opportunity to selectively reduce the number of astrocytes after birth and assess their effects on vessel development. This study will unmask cellular mechanisms essential for proper brain angiogenesis.

1-A-15 *A common epigenetic pathway regulates both neural stem cell reprogramming and differentiation by controlling acetylation shift and Sox2 nuclear-cytoplasmic trafficking*

Charvi Syal[1], Sailendra Nath Sarma[1], Ayden Gouveia[1], Matthew Seegobin[1], Jing Wang[1]

[1]Ottawa Hospital Research Institute

Understanding direct signals that control epigenetic regulation to determine cell fate provides fundamental knowledge to develop pharmacological approaches to regenerate the injured brain. Here we report that an atypical protein kinase C (aPKC)-mediated Ser436 phosphorylation of CBP, a histone acetyltransferase, coordinates an acetylation shift between Sox2 and histone 2B (H2B) and Sox2 nuclear-cytoplasmic trafficking, thus modulating neural stem cell (NSC) reprogramming and differentiation. Using an ischemic stroke model combined with a phospho-null murine strain (CbpS436A), we show that inactivation of the aPKC-CBP pathway by an AMPK inhibitor, compound C, enhances H2B acetylation while reducing Sox2 acetylation, thus

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accelerating Sox2 nuclear import in ischemia-activated pericytes to facilitate their reprogramming into NSCs. In contrast, activation of the aPKC-CBP pathway by an AMPK activator, metformin, enhances Sox2 acetylation while reducing H2B acetylation, elevating Sox2 nuclear export to promote neuronal differentiation of NSCs. Together, this study suggests that pharmacological approaches targeting the aPKC-CBP pathway can regulate acetylation shift and Sox2 nuclear-cytoplasmic trafficking to modulate both, NSC reprogramming from ischemia-activated pericytes, and further differentiation of the induced-NSCs into newborn neurons. This discovery will provide fundamental knowledge to develop therapeutic strategies targeting in vivo cellular reprogramming/differentiation to promote local regeneration at the site of brain injury.

1-A-16 *Myelin-associated glycoprotein binds to discoidin domain receptor 1 and induces activation of latent TGFβ in CNS neurons*

Matsya Thulasiram[1], Justine Cadieux[1], Dennis Drewnik[1], Sari Hannila[1]

[1]University of Manitoba

Following spinal cord injury, axonal regeneration is limited by inhibitory molecules in the central nervous system (CNS), leading to permanent motor and sensory deficits. CNS myelin proteins such as myelin-associated glycoprotein (MAG) are major factors contributing to this regenerative failure. MAG typically mediates inhibition through the Nogo receptor 1 (NgR1) complex, but we have previously shown that MAG also induces Smad2 signaling. Here we report that soluble MAG activates the transforming growth factor β (TGFβ) receptor in cerebellar granule neurons (CGN) and that this effect does not involve signaling through canonical MAG receptors such as NgR1, paired immunoglobulin receptor B, and low density lipoprotein receptor-related protein 1. By contrast, CGN treated with MAG showed rapid and sustained increases in active TGFβ when samples of conditioned media were analyzed by enzyme-linked immunosorbent assays and Western blotting. This suggests that MAG may be inducing Smad2 phosphorylation through the activation of latent TGFβ at the cell surface, leading to autocrine/paracrine activation of the TGFβ receptor. Using LRC-TriCEPS and immunoprecipitation, we then identified discoidin domain receptor 1 (DDR1) as a novel receptor for MAG. DDR1 activates matrix metalloproteases that have known roles in the activation of latent TGFβ, and so, we propose that MAG binding to DDR1 may be responsible for the increases in TGFβ levels observed in our experiments, and perhaps more importantly, the upregulation of TGFβ that occurs after spinal cord injury.

1-A-17 *A postembryonic role for dmbx1a in zebrafish retinal growth, development and maintenance*

Amanda Miles[1], Vince Tropepe[1]

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[1]University of Toronto

Dmbx1 is a paired-like homeobox transcription factor known to function as a transcriptional repressor. Transient gain and loss of function studies in zebrafish have shown that dmbx1 is important for promoting cell cycle exit of retinal progenitor cells (RPCs) during embryonic retinal development. The importance of dmbx1 in the post-embryonic, mature zebrafish retina, however, is unknown. To examine the long-term consequences of dmbx1 loss of function, we generated a dmbx1a mutant harbouring a 25bp deletion, using CRISPR-Cas9 technology. We found that these mutants have relatively normal gross morphology, except for a poorly developed swim bladder, and die by 15dpf. Analysis of the retina indicates that dmbx1a mutants develop a fully differentiated, laminated retina by 3dpf. However, by 10dpf dmbx1a mutants have a significantly smaller retina. Mild defects in proliferation and increased cell death observed at 3dpf in the mutants partially account for this phenotype. However, our analyses indicate that defects in the contribution of newly generated cells from the post-embryonic CMZ stem cell population contribute significantly to the small eye phenotype. Dmbx1 loss, however, did not appear to affect Muller glial stem cell function in response to a lesion. Further analyses on 10dpf retina by immunohistochemistry and TEM indicate that photoreceptors become dystrophic in the mutants. These results indicate that dmbx1a is important post-embryonically, for continued retinal growth and maintenance of differentiated photoreceptor morphology.

1-A-18 *Activating EGFR-induced signalling pathways recruits qNSCs in the adult brain*

Loïc Cochard[1], Sandra Joppé[1], Louis-Charles Levros[1], Anne Aumont[1], Karl Fernandes[1]

[1]University of Montreal

Neural stem cell (NSC) activity is altered in many abnormal biological contexts, such as neurodegenerative diseases, potentially contributing to disturbances in cognitive functions and brain repair capacity. The epidermal growth factor receptor (EGFR) is expressed by actively proliferating NSCs (aNSCs) but not by quiescent NSCs (qNSCs). We hypothesized that activity of qNSCs can be promoted by selectively stimulating signalling pathways downstream of EGFR. To test this, we: i) dissected the roles of selected EGFR-induced signaling pathways in aNSC/progenitor functions in vitro (survival, proliferation, differentiation), and ii) determined whether activation of EGFR-induced signaling pathways in EGFR-negative qNSCs is sufficient to promote their proliferation in vivo. Using the colony-forming neurosphere method, we first isolated and expanded forebrain NSCs and used these aNSC/progenitor cultures to examine the impact of pharmacological or genetic signaling pathway manipulations. Loss-of-function analyses of individual EGFR-induced pathways revealed distinct roles of the AKT, ERK, and mTOR pathways in the processes of stem/progenitor survival, proliferation, and/or differentiation. Since qNSCs do not express EGFR, we electroporated qNSCs in vivo with a constitutively active EGFR: this was sufficient to activate their EGFR-induced signaling, stimulate their proliferation, and increase their

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contribution to the olfactory bulbs. These studies provide insights into potential strategies for recruiting dormant NSCs to promote brain repair.

1-A-19 *Microglia interact with hypothalamic progenitors during development and are required for proper energy balance*

Jessica Rosin[1], Deborah Kurrasch[1]

[1]University of Calgary

Microglia are the resident mononuclear phagocytic immune cells of the CNS, and are primarily responsible for responding to neural insults and disposing of cellular debris. However, over the last decade studies are showing that microglia are highly dynamic cells involved in various critical neurodevelopmental processes. We set out to study microglia dynamics in the embryonic hypothalamus given that the hypothalamus is critical for maintaining homeostatic processes. Using slice culture and time-lapse imaging we showed that hypothalamic microglia are highly dynamic during embryogenesis, constantly surveying their environment and often interacting with radial glia precursor cells that line the third ventricle and are responsible for generating hypothalamic neurons, oligodendrocytes, astrocytes, and tanycytes. Moreover, given that microglia colonize the embryonic brain alongside key steps of hypothalamic development, we wanted to test whether microglia are required for the proper establishment of this brain region. To eliminate microglia from the fetal brain, we treated pregnant dams with the Csf1r inhibitor PLX5622, as Csf1r is expressed by microglia and is required for their proliferation, differentiation, and survival. Embryonic microglia depletion resulted in a decreased litter size, as well as an increase in the number of pups that died within the first two postnatal days of life. In pups that survived, the elimination of microglia in the fetal brain resulted in a decrease in the number of POMC neurons and a concomitant accelerated weight gain, suggesting that microglia could be important for the development of hypothalamic satiety centers. Taken together, these data demonstrate an important role for microglia during the development of the embryonic hypothalamus.

B - Neural excitability, synapses, and glia: Cellular mechanisms

1-B-20 *Regional heterogeneity of vimentin- and GFAP-immunoreactive astrocytes*

Liam O'Leary[1], Claudia Belliveau[1], Maria-Antonietta Davoli[2], Naguib Mechawar[1]

[1]McGill University, [2]Douglas Institute, McGill University

This study characterizes the distribution and morphology of astrocytes in various human and mouse brain regions. We hypothesized that two intermediate filament proteins expressed by

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astrocytes---vimentin (VIM) and glial fibrillary acidic protein (GFAP)---would label complementary populations of astrocytes. To test this, we performed fine neuroanatomical analysis of astrocytes immunoreactive (-IR) for VIM or GFAP in postmortem brain samples provided by the Douglas-Bell Canada Brain Bank from 8 healthy individuals and in brains from 6 adult C576BL mice. Fresh-frozen tissue from prefrontal and primary visual cortex, caudate nucleus, and mediodorsal thalamus was postfixed and immunostained for brightfield (single labeling) or immunofluorescence (double labeling) using anti-VIM and anti-GFAP antibodies. Densities and morphometric properties of astrocytes were examined using StereoInvestigator and Neurolucida (MBF Bioscience). Immunofluorescence indicated that GFAP is expressed in proportionally fewer human (5%) than mouse (50%) VIM-IR cells. For all human brain regions, VIM-IR cells were larger but fewer in number than GFAP-IR cells, however, both cell populations were regionally heterogeneous. Protoplasmic astrocyte morphology varied across species more for VIM-IR cells than for GFAP-IR cells. Furthermore, we also observed strong regional differences in CD31-IR vascular density that may account for regional differences in VIM-IR and GFAP-IR number and morphology. These findings highlight the diversity of astrocytes across markers, regions and species.

1-B-21 *Sex- and region-specific changes in neural network activity in stress-susceptible rats in the chronic unpredictable stress model of depression*

Rachel-Karson Theriault[1], Joshua Manduca[1], Melissa Perreault[1]

[1]University of Guelph

Major depressive disorder (MDD) is twice as prevalent in women than in men. Aberrant neural oscillatory activity is an emerging mechanism underlying MDD, however its role in female susceptibility remains unknown. The present study evaluated sex differences in stress-induced circuit dysfunction using the chronic unpredictable stress (CUS) model of MDD. Male and female Wistar rats were stereotactically implanted with electrodes into the prefrontal cortex (PFC), cingulate cortex (Cg), nucleus accumbens (NAc), and dorsal hippocampus (dHIP). All rats were then exposed to CUS and local field potential recordings taken throughout, with forced swim test (FST) and sucrose preference test assessed weekly. Animals were labeled as stress-resilient or -susceptible based on immobility changes in FST. A shorter CUS exposure was sufficient to induce depressive-like behaviour in stress-susceptible females (3 weeks) compared to males (5 weeks). Stress-susceptible male and female rats showed increased delta power in the NAc and Cg, as well as reduced theta power in all regions; changes not exhibited by resilient rats. These theta power reductions were significantly greater in susceptible females versus male rats. FST immobility time was significantly correlated with dHIP delta and theta power in both sexes, and with delta and theta power in the NAc and Cg selectively in the female rats. These findings suggest

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that the manifestation of depression-like behaviour is accompanied by sex- and frequency-specific alterations in spectral power in brain regions known to be associated with MDD.

1-B-22 *Endothelial NMDA receptors regulate cerebral hemodynamics and blood flow in awake behaving mice*

Adam Hogan-Cann[1], Ping Lu[1], Andrea Globa[2], Shernaz Bamji[2], Christopher Anderson[1]

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

Functional hyperemia (FH) ensures that active brain regions receive proportional delivery of blood flow. However, neuro-endothelial coupling remains as a key conceptual deficit in understanding FH. We have observed that isolated middle cerebral artery segments free of neurons dilate in response to NMDA receptor agonists in a manner that requires functional endothelium and eNOS. We also found that two-photon photolysis of caged astrocyte Ca2+ in mouse cortical slices led to NMDA receptor and eNOS-dependent vasodilation. The current study was designed to test the possibility that endothelial NMDA receptors (eNMDARs) participate in neurovascular coupling (NVC) by measuring the hemodynamic responses in awake, head-fixed mice following sensory stimulation. To distinguish between neuronal and eNMDARs we created conditional eNMDAR loss of function mice that were characterized by greater than 50% loss of endothelial GluN1 (eGluN1) expression. Laser-Doppler flowmetry revealed that whisker stimulation increased CBF in the somatosensory cortex of wild-type mice. This response was dramatically impaired in eGluN1 deficient mice. Using two-photon microscopy, we measured vascular lumen diameter and red blood cell (RBC) velocity to better understand the dynamics of neurovascular coupling at the single vessel level in awake mice. In eGluN1 knockdown mice, the increase in lumen diameter and RBC velocity following whisker simulation was reduced relative to controls. Our results identify a novel mechanism of neuro-endothelial coupling by showing that eNMDARs mediate activity-dependent, NVC.

1-B-23 *Psychological stress modulates synaptic mechanisms for immune-induced HPA axis activation*

Meagan Wiederman[1], Wataru Inoue[2]

[1]Western University, [2]University of Western Ontario

Immune-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis elevates the anti-inflammatory hormone, glucocorticoid, ensuring the effective resolution of the inflammatory response. However, this important anti-inflammatory mechanism can be impaired by prior exposures to psychological stress. Here, we investigate potential synaptic mechanisms for this

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neuro-immune interaction. We used whole-cell patch clamp electrophysiology in acute brain slices from mice and recorded from HPA axis output neurons [corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN)]. First, we found that prostaglandin E2 (PGE2), a major mediator of immune-induced HPA axis activation, strongly depresses GABA-mediated inhibitory synaptic transmission to PVN-CRH neurons via EP3 receptor subtype: this mechanism likely disinhibits PVN-CRH neurons and thereby excites the HPA axis. When we repeated the same experiments in slices from acutely stressed mice, the PGE2 response became highly variable where about half of the recorded cells responded with depression while the other half responded with potentiation. Using pharmacology for different EP receptor subtypes (EP1-4), we found that EP3 receptor-mediated GABA synapse depression was intact after stress. By contrast, we found that stress unmasks GABA synapse potentiation mediated by EP2 and EP4 receptors that can override EP3-mediated depression at some synapses. Our research identifies a potential mechanism where prior psychological stress alters immune-induced HPA axis activation.

1-B-24 *Novel rat monoclonal antibody against murine P2RY12 for specific detection and isolation of microglia*

Anna Cartier[1], Lasse Dissing-Olesen[2], Hong Zhang[1], Juan Moyron-Quiroz[1], Kenya Cohane[1], Miguel Tam[1], Beth Stevens[2], Peggy Taylor[1]

[1]BioLegend, [2]Children's Hospital Boston

Dysregulation of microglia function has been associated with neuropsychiatric and neurodegenerative disorders. A major limitation in understanding microglial contribution to cellular processes and their role in disease has been the lack of tools to distinguish these cells from other myeloid cells. In an effort to produce a novel, microglia-specific tool, we have generated a rat monoclonal antibody against murine Purinergic Receptor P2Y12 (P2RY12), a highly selective marker for microglial cells that enables immunostaining in histological sections as well as isolation of these cells by FACS and magnetic nanobeads. The specificity of the P2RY12 antibody was validated in single cell homogenates from various organs analyzed by flow cytometry by gating cells on CD45, and analyzing for P2RY12 and CX3CR1 expression. Immunohistochemistry was used to further validate the antibody in tissue sections derived from mouse brain. Furthermore, we validated the utility of the P2Y12 antibody for use in combination with BioLegend's MojoSort magnetic cell separation system, to isolate microglia with high purity and yield. In addition, we show that LPS injection in mice, which causes systemic inflammation, leads to downregulation of P2RY12, a protein known to be expressed under homeostatic conditions. With our studies we demonstrate the specificity, versatility, and utility of a novel and unique rat anti-mouse P2RY12 antibody that will facilitate research in microglia and their role in the CNS.

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1-B-25 *Characterizing microglial and macrophage-mediated repair of cerebral microbleeds in a mouse model of type 1 diabetes mellitus*

Eslam Mehina[1], Stephanie Taylor[2], Sun Eui Choi[3], Craig Brown[1]

[1]University of Victoria, [2]Deutsches Zentrum für Neurodegenerative Erkrankungen, [3]University of Toronto

Microglia, the innate immune cells of the brain, respond to cellular damage including ruptures in small blood vessels, termed cerebral microbleeds (CMBs). Type 1 diabetes mellitus is a risk factor for vascular damage, including CMBs. Our previous work showed that microglial responses are perturbed in the diabetic brain. Since vascular repair evolves over days, it remains unclear how diabetes impacts this process over the long-term. Here we use 2-photon microscopy to image microglial responses and vascular repair in vivo in type 1 diabetic male mice following induction of CMBs. In contrast to nondiabetic mice where 100% of ablated vessels (43/43 vessels) regained blood flow, ~20% of vessels from insulin-treated and untreated diabetic mice were pruned within 3 days. To assess the contribution of microglia versus circulating leukocytes in vessel repair after CMB, we depleted each cell type using the PLX5622 diet (microglia) or clodronate liposomes (circulating leukocytes). By depleting microglia, we discovered vessel pruning increased from 0 to 20% and 20 to 27% in nondiabetic and diabetic mice, respectively, suggesting that microglia contributed to vascular repair. By contrast, eliminating circulating phagocytic leukocytes reduced the rate of vessel pruning in diabetic animals from 20 to 7%, without compromising repair in nondiabetic animals. We are investigating factors regulating phagocytic activity in microglia and macrophages after vascular injury to assess whether diabetes perturbs these processes. Funded by NSERC, Vanier CGS, CIHR, and Heart and Stroke Foundation.

1-B-26 *Role of NMDA Receptor-initiated, PARP-1/TRPM2 in driving Sustained Microglial Activation*

Prajwal Raghunatha[1], Natalie Lavine[1], Tiina Kauppinen[1], Michael Jackson[1]

[1]University of Manitoba

An important component of neurodegenerative disorders, like AD, is the prolonged inflammatory response driven by continuous microglial poly(ADP-ribose) polymerase-1 (PARP-1) activation. However, the mechanism maintaining PARP-1 activity remains elusive. PARP-1 activity requires Ca2+ influx, which could be through microglial N-methyl D-aspartate receptors (NMDARs). Notably, PARP-1 mediated ADPR production causes activation of Ca2+ permeable non-selective cation channel, transient receptor potential melastatin-2 (TRPM2). Hence, we hypothesize that NMDAR activation initiates PARP-1 mediated ADPR production and TRPM2 activation. This leads to TRPM2-dependent, self-sustaining PARP-1 activation, which promotes pro-inflammatory responses. To test this hypothesis, we used primary murine cortical microglia cultures. Whole-cell

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recordings from NMDA treated microglia showed functional TRPM2 currents, which were blocked by inhibitors of NMDAR and PARP-1, reflecting NMDAR initiated and PARP-1-dependent TRPM2 recruitment. Calcium imaging of NMDA treated microglia confirmed the ionotropic function of microglial NMDARs. TRPM2 and pro-inflammatory marker inducible nitric oxide synthesis (iNOS) transcripts were upregulated in NMDA treated microglia. In addition, we observed nitric oxide (NO) release in WT microglia, but not upon TRPM2 deletion, or in the presence of NMDAR and PARP-1 inhibitors, showing NO release is PARP-1/TRPM2 dependent. Combined, these results demonstrate NMDAR initiated activation of PARP-1 and TRPM2, thereby maintaining prolonged microglial inflammatory responses.

1-B-27 *Selective potentiation of evoked excitatory transmission onto dentate granule cells during ketamine-induced rapid antidepressant response*

Haider Altimimi[1], Pei-Yi Lin[1], Natali Chanaday[1], Lisa Monteggia[2], Ege Kavalali[2]

[1]University of Texas Southwestern Medical Center, [2]Vanderbilt University

Major depressive disorder (MDD) is a common neuropsychiatric condition primarily treated by pharmacotherapeutics targeting various forms of monoaminergic neurotransmission. However, the antidepressants available to date are inefficacious for a large proportion of MDD patients, and moreover require a prolonged treatment window of weeks for therapeutic potential to be revealed, limiting their use in urgent cases of suicidal patients. Ketamine, an NMDA receptor antagonist, has emerged as a highly promising therapeutic when administered at subanesthetic doses, because of its rapid antidepressant effect which in many patients occurs within two hours. How subanesthetic doses of ketamine impact neuronal circuitry to achieve a rapid antidepressant effect is presently unclear. To address this, we investigated synaptic transmission in the hippocampus, a brain region where neurons and synapses are vulnerable to chronic stress and depression, and which is critical for the antidepressant response. Two hours following subanesthetic ketamine administration, we found glutamatergic transmission to be greatly potentiated, specifically in dentate gyrus (DG). Electrophysiological interrogation of the mechanism of ketamine-induced potentiation did not reveal significant alterations in standard pre- or postsynaptic markers of synaptic efficacy or spontaneous neurotransmission. Overall, these observations are consistent with the premise that ketamine administration selectively unsilences evoked excitatory neurotransmission in a subset of synapses that can otherwise maintain spontaneous release.

1-B-28 *Contribution of voltage gated calcium channels in astrocytic glutamate signalling*

Mitra Tabatabaee[1], Frederic Menard[1]

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[1]UBC Okanagan

Glutamate is the major excitatory neurotransmitter in our central nervous system. It also acts as an active signaling molecule for astrocytes that leads to filopodiagenesis and a prompt internal calcium rise. While glutamate receptors are known to be expressed in astrocytes, they have not been conclusively shown to directly trigger downstream events upon glutamate sensing in glia. In our search for receptors that can couple glutamate sensing with calcium influx in astrocytes, we identified voltage gated calcium channels (Cav's). Astrocytes being non-excitable cells, the reason for their expression of Cav's is unclear. Yet, local and long-range calcium signalling in astrocytes is well established, and we hypothesized that Cav's may be involved. In addition, emerging roles for Cav's α2δ subunit support a plausible role in cellular signal transduction. We studied systematically the possible contribution of Cav-α2δ in astrocytic glutamate signalling. proteomic searches on a range of glutamate sensors, revealed highly conserved motifs with the Cav-α2δ genes known to be expressed in astrocytes; an observation supported by pharmaceutical studies on Cav-α2δ blockers (e.g., gabapentinoids). Our investigations on the function of Cav-α2δ show that gabapentinoids block the extension of processes in astrocytoma cell lines that lack other functional glutamate receptors. These pharmacologic observations are being confirmed in Cav-α2δ knock-out glia. We also demonstrate that different subunits of Cav's are associated with astroglial glutamate signalling using novel 3D cell cultures and

1-B-29 *Protein synthesis requirement for the late phase of netrin-1 induced synaptic potentiation*

Jeanne Madranges[1], Stephen Glasgow[2], Ian Beamish[1], Edward Ruthazer[2], Timothy Kennedy[2]

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

Long-term potentiation (LTP) is an activity dependent form of plasticity that strengthens glutamatergic synapses and serves as a cellular model of learning and memory formation. We have recently demonstrated that netrin-1, a secreted chemotropic cue that regulates cell migration, axon guidance and synaptogenesis during neural development, is required and sufficient for LTP at the Schaffer collateral synapse through rapid recruitment of GluA1 AMPA receptors. Previous findings indicate that netrin-1 can rapidly initiate protein synthesis through local translation in neurons, suggesting that netrin-1 may regulate long-term changes in synapse strength through translation of synaptic proteins. Here, we demonstrate that transient bath application of netrin-1 results in a persistent potentiation of synaptic responses for >4 hours in adult hippocampal brain slices, indicating that netrin-1 induced synaptic strengthening is long-lasting. Investigating a role for translation, our findings provide evidence that the long-lasting synaptic plasticity induced by netrin-1 requires de novo protein synthesis.

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1-B-30 *L-type calcium channels modulate the firing pattern of the basolateral amygdala principal neurons*

Yiming Zhang[1]

[1]University of British Columbia

Gain-of-function mutations in L-type calcium channels (LTCCs) have been associated with neurodevelopmental disorders including autism spectrum disorders (ASD). However, to date, the functional role of LTCCs in regulating neuronal excitability and homeostasis of brain circuits during early development has not been explored. Whole-cell recordings from brain slices were performed to study the acute and chronic effects of (S)-Bay K8644 on the excitability of basolateral amygdala (BLA) principal neurons around a critical brain developmental period in rats (P7 - P21). The results show that acute LTCC agonist application to post-natal day 7 (P7) slices (immature neurodevelopmental stage) increased the excitability properties of BLA neurons as indicated by an altered firing frequency, enhanced plateau potential and reduction of spike frequency adaptation. Contrastingly, LTCC agonist application resulted in an increase in bursting and rebound firing in P21 neurons (close to maturity). Stereotaxic single injection of (S)-Bay K8644 in the amygdala area at P7 evoked long-lasting effects detected in BLA neurons at P21 including a higher firing frequency, enhanced rebound firing and increased burst firing. Experiments to further examine the underlying mechanisms of these effects are underway. Dysfunction of the BLA has been implicated in the etiology of psychiatric disorders and the findings support the notion that enhanced increases in LTCC activity during key neurodevelopment periods could potentially underlie alterations of neuronal circuitry associated with disorders such as ASD.

1-B-31 *Sex-specific adaptations to chronic stress in NAc- and VTA-projecting pyramidal neurons of the mPFC*

Thibault Bittar[1], Jose Cesar Hernandez Silva[1], Khaled Abdallah[1], Christophe Proulx[1], Benoit Labonté[1]

[1]CERVO Brain Research Centre

Background. Males and females respond differently to chronic stress. The medial prefrontal cortex (mPFC) is part of a complex circuit controlling stress response by sending projections to different limbic structures including the nucleus accumbens (NAc) and ventral tegmental area (VTA). However, whether these pathways are differently involved in the expression of depressive-like behaviors following chronic stress in males and females is still unclear. Methods. Chronic variable stress (CVS) was used to induce a stress phenotype in males and females. We injected retrograde adeno-associated viruses encoding different fluorophores in the NAc and VTA of male and female mice to label both pathways and assess the spontaneous activity and morphological adaptations of mPFC neurons in stressed males and females. Results. CVS induced depressive-like behaviors

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in males and females. Our viral approach allowed us to differentiate mPFC neurons according to their projection. Stressed females exhibited a significantly higher frequency in spontaneous excitatory postsynaptic currents in both neuronal populations. Conversely, we observed a trend toward a lower frequency of spontaneous inhibitory postsynaptic currents in both populations in stressed males. Consistent alterations in dendritic arborization and spine density were found in NAc- and VTA-projecting neurons. Conclusion. Our results suggest that chronic stress impacts the cortico-striatal and -tegmental pathways differently in males and females through sex-specific functional and morphological alterations in mPFC pyramidal neurons.

1-B-32 *An in vitro investigation of amyloid-β oligomer effects on microglia pro-inflammatory activation and bioenergetics using stable synthetic oligomers*

Sarah Louadi[1], Peter Overby[2], Judith Silverman[1], Ebrima Gibbs[1], James Johnson[2], Neil Cashman[1]

[1]University of British Columbia, Djavad Mowafaghian Centre for Brain Health, [2]University of British Columbia

The consistent inflammatory state observed in Alzheimer's disease (AD) has sparked interest in the role of brain immune cells, and more specifically microglia, in AD pathology. However, the role that Amyloid- beta (Aβ) aggregates play in this process remains unclear, as they are found to exert opposing effects on microglia function. We used stabilized Aβ tetramers at nanomolar concentrations (0.1-50 nM) to test the effects of small order oligomers (AβO) on microglia inflammatory response, viability, and metabolism in vitro at 3-24hrs. Nitric Oxide (NO) and TNF-α levels in addition to cell morphology were used as indicators of cell activation after 24hrs. Cell viability was tracked with the lactate dehydrogenase cytotoxicity assay, propidium iodide staining detection by flow cytometry, and manual counts of trypan blue-stained cells. To assess metabolic activity, ATP levels and oxygen consumption rate were assessed real time using the Seahorse XF Analyzer (Agilent, USA). The MTT cell metabolic activity assay was also used at all time points. While the AβOs did not cause pro-inflammatory activation, they did induce a significant reduction in NAD(P)H-dependent oxidoreductase activity. This decrease was not accompanied by cell death in the time course of the experiment, and a further investigation of the bioenergetic status of these cells shows that the AβOs interact with the ETC through ATP synthase. These results suggest that AβOs may induce a state of quiescence in these cells by blocking their metabolic activity and potentially hinder their inflammatory response.

1-B-33 *Synaptopodin is necessary for homeostatic upscaling*

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Jennifer Boateng[1], Melanie Chan[1], Jelena Popic[1], Philip Chang[1], Anne McKinney[1]

[1]McGill University

Mechanisms that underlie learning and memory can destabilize neural networks when left uncontrolled. Homeostatic scaling is a process that maintains the stability of neural networks through the trafficking of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) at excitatory synapses. Dendritic spines possess the relevant cellular machinery for AMPAR trafficking and within a subset of larger dendritic spines is synaptopodin, an actin-associated protein. While synaptopodin has been documented to promote Hebbian plasticity and is involved in AMPAR trafficking, its function within the context of homeostatic synaptic scaling remains unknown. Here, we set out to investigate the role of synaptopodin in homeostatic scaling. Scaling was induced by treating wildtype (WT) and synaptopodin knockout (SPKO) organotypic hippocampal cultures with tetrodotoxin for 3-4 days. Whole cell electrophysiology was used to measure AMPA mediated miniature excitatory postsynaptic currents (mESPC). While WT CA1 pyramidal neurons scaled up the amplitude of mESPC, SPKO neurons were unable to undergo upscaling. Release of tumor necrosis factor alpha (TNFα), a factor necessary for upscaling, was observed in WT neurons but not SPKO neurons during chronic inactivity. The addition of exogenous TNFα did not restore scaling in SPKO neurons despite the expression and activation of the functional receptor. The findings from this study contribute to the evolving literature on synaptic scaling and enhance our knowledge of the potential mechanisms involved.

1-B-34 *Cholinergic signalling dysregulation in the prefrontal cortex of the TgF344 rat model of Alzheimer's disease*

Saige Power[1], Sridevi Venkatesan[1], Daniel Sparks[1], Janice McNabb[1], JoAnne McLaurin[2], Evelyn Lambe[1]

[1]University of Toronto, [2]Sunnybrook Research Institute

"If you don't attend, you can't encode" (Romberg et al., 2013). Improving the early disruption of attention in Alzheimer's Disease is a potentially high-impact treatment goal. Cholinergic signalling in prefrontal cortex is vital for attentional control and executive function, yet much remains unknown about the cellular mechanisms of attentional dysfunction in early to mid-disease AD. Here, we investigate the TgF344 rat model of AD that has advantages over previous models because it more closely replicates the molecular and behavioural trajectory of human AD pathology. Starting at the earliest stage and continuing into the equivalent of mid-stage disease, we probe cognition and prefrontal circuitry using behavioural experiments and electrophysiological investigation in brain slices of prefrontal cortex. TgF344 rats are cognitively normal up to 9 months of age. Thereafter the AD rats start to exhibit deficits in executive function in comparison to non-transgenic littermates. Our electrophysiological experiments probe the

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intrinsic membrane properties of prefrontal neurons and their response to cholinergic modulation. Aberrant responses to acetylcholine are observed in the TgF344 rat model compared to wild-type controls, and ongoing experiments are probing the underlying pharmacological differences between the genotypes. These findings will provide insight into the molecular progression of cholinergic dysfunction in a high-fidelity model of human AD, improving our understanding of important deficits in executive function.

1-B-35 *Hippocampal long-term depression in the presence of calcium-permeable AMPA receptors*

Feng Cao[1], Zhengping Jia[1]

[1]The Hospital for Sick Children

The GluA2 subunit of AMPA glutamate receptors (AMPARs) has been shown to be critical for the expression of NMDA receptor (NMDAR)-dependent long-term depression (LTD). However, in young GluA2 knockout (KO) mice, this form of LTD can still be induced in the hippocampus, suggesting that LTD mechanisms may be modified in the presence of GluA2-lacking, Ca2+ permeable AMPARs. In this study, we examined LTD at the CA1 synapse in GluA2 KO mice by using several well-established inhibitory peptides known to block LTD in wild type rodents. We showed that while LTD in the KO mice is still blocked by the PICK1 peptide pepEVKI, it becomes insensitive to the NSF peptide pep2m. In addition, the effects of actin and cofilin inhibitory peptides were also altered. These results indicate that in the absence of GluA2, LTD expression mechanisms are different from those in wild type animals, suggesting that there are multiple molecular processes enabling LTD expression that are adaptable to physiological and genetic manipulations.

1-B-36 *Panx1 knockout fish as a model to investigate seizure activity*

Paige Whyte-Fagundes[1], Nickie Safarian[1], Daria Taskina[1], Christiane Zoidl[1], Peter Carlen[2], Georg Zoidl[1]

[1]York University, [2]Krembil Research Institute

Altered GABAergic and purinergic signaling are implicated in altering neuronal excitation leading to the transition from normal brain function to seizures. Evidence has emerged suggesting that Panx1, an interacting partner with purinergic (P2) receptors, has dual roles either increasing seizure activity or acting as an anticonvulsant. To resolve this conflict, zebrafish genetically modified with TALEN technology to lack Panx1 expression were used to study the mechanism behind the involvement of Panx1 in seizures. RNA-Seq analysis of Panx1 knockout fish

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demonstrated a regulation of GABA receptor subtypes as well as various P2 receptor subtypes; consistent with reports demonstrating Panx1 and P2R interactions altering excitability in various cell types. Therefore, the mechanistic involvement of Panx1 and P2Rs was tested by in vivo electrophysiological field recordings taken from forebrain and tectal regions of immobilized zebrafish larvae in an experimental model of seizures induced by pentylenetetrazol (PTZ). These results were paired with standard behavioural testing to classify seizure stages. Together, results revealed that targeting Panx1 and P2Rs can mediate seizure activity and improve seizure outcomes. With almost 40% of epileptics having recurrent seizures uncontrolled by medication, these zebrafish lines represent a toolbox for exploring seizures from genes to behaviour; highlighting the interplay of Panx1 and P2Rs at the core of these investigations as an experimental platform for translational drug discovery.

1-B-37 *Palmitoylation-dependent control of neuronal excitability by ion channel clustering at the axon initial segment*

Shaun Sanders[1], Luiselys Hernandez[1], Santi Karnam[1], Heun Soh[2], Anastasios Tzingounis[2], Gareth Thomas[1]

[1]Temple University, [2]University of Connecticut

Precise control of neuronal excitability is essential for normal behaviour and cognition, while aberrant excitability is a hallmark of many neurological diseases. One key factor that controls the threshold of excitability is the clustering of voltage-gated ion channels at the Axon Initial Segment (AIS), but how such clustering is regulated is not fully understood. Ion channel clustering at other subcellular locations is often controlled by modification of Membrane-Associated Guanylate Kinase (MAGUK) family 'scaffold' proteins with the lipid palmitate, a process called palmitoylation. Using unbiased screening we identified PSD-93, the only MAGUK family member that localizes to the AIS, as a direct interactor and substrate of the palmitoyl acyltransferase (PAT) ZDHHC14. Lentiviral-mediated Zdhhc14 knockdown in cultured hippocampal neurons markedly reduced palmitoylation and AIS targeting of PSD-93. A key role of PSD-93 at the AIS is to cluster Kv1 family potassium channels, which are themselves palmitoylated. Consistent with this model, ZDHHC14 expression mirrors that of Kv1 channels during neurodevelopment, and Zdhhc14 knockdown reduces Kv1 channel palmitoylation and AIS targeting, and concomitantly increases excitability. These findings provide new insights into the regulation of ion channel clustering at the AIS, with broad implications for our understanding of physiological regulation of excitability and its dysfunction in conditions such as epilepsy.

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1-B-38 *Macrophages regulate Schwann cell maturation after nerve injury*

Jo Stratton[1], Alex Holmes[1], Jeff Biernaskie[2]

[1]Hotchkiss Brain Institute, [2]University of Calgary

Pro-regenerative macrophages are well known for their role in promoting tissue repair; however, their specific roles in promoting regeneration of the injured nerve are not well defined. Specifically, how macrophages interact with Schwann cells following injury during remyelination has been largely unexplored. We demonstrate that after injury, including in humans, macrophages function to clear debris and persist within the nerve microenvironment. Macrophage ablation immediately preceding remyelination results in an increase in immature Schwann cell density, a reduction in remyelination, and long-term deficits in conduction velocity. Targeted RNA-seq of macrophages from injured nerve identified Gas6 as one of several candidate factors involved in regulating Schwann cell dynamics. Functional studies show that the absence of Gas6 within monocyte lineage cells impairs Schwann cell remyelination within the injured nerve. These results demonstrate a role for macrophages in regulating Schwann cell function during nerve regeneration and highlight a molecular mechanism by which this occurs.

1-B-39 *Regional differences in ventral tegmental area neuronal plasticity in a mouse model of neuropathic pain*

Shuo Huang[1], Stephanie Borgland[1], Gerald Zamponi[1]

[1]University of Calgary

The ventral tegmental area (VTA) is one of the main brain regions harboring dopaminergic (DA) neurons, and plays an important role in reward and reinforcement. Recent studies have indicated that DA neurons not only respond to reward, but also to noxious stimuli. Furthermore, the VTA DA neurons undergo plasticity during chronic pain. The ventral and lateral VTA neurons project to different brain areas, and have been characterized by means of their distinct electrophysiological properties. In this study, we demonstrate that ventral and lateral VTA DA neurons undergo differential plasticity in a neuropathic pain model. Neurons in the lateral VTA of neuropathic pain mice exhibit decreased spontaneous firing frequency and input resistance, indicating reduced neuronal excitability. Neurons in the medial VTA showed increased excitability including increased spontaneous firing and frequency-current relation slope. Hence, we demonstrate the existence of regional differences in nerve injury-induced plasticity within the VTA, and provide further evidence for the role of the VTA in pain signalling.

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1-B-40 *7b-hydroxycholesterol-induced cell death, oxidative stress, and fatty acid metabolism dysfunctions attenuated with sea urchin egg oil*

Amira zarrouk[1], Yosra Ben Salem[2]

[1]Faculté de médecine de Sousse, [2]Laboratoire des Interfaces et des Materiaux Avances (LIMA), Faculté des Sciences de Monastir

Some oxysterols are associated with age-related diseases including neurodegenerative diseases. Among these oxysterols, 7b-hydroxycholesterol (7b-OHC) is often found at increased levels in patients. Thus, it is important to identify molecules to prevent 7b-OHC-induced side effects. Murine oligodendrocytes (158N) were cultured in the presence of 7b-OHC (20mg/mL, 24 h) with or without a natural oil extracted from sea urchin eggs (SUEO). The chemical composition of this oil was determined using 31P NMR and GC-MS. This oil was used to reduce 7b-OHC-induced side effects (160mg/mL 2h before addition of 7b-OHC). Photometric methods were used to analyze cell viability, antioxidant enzyme activities (SOD and GPx), as well as the generation of lipid and protein oxidation products (malondialdehyde (MDA), conjugated dienes (CDs), carbonylated proteins (CPs)). GC was used to determine cellular fatty acid profile. With 7b-OHC, an induction of cell death associated with oxidative stress (alteration of GPx and SOD activities) was observed; an overproduction of lipid peroxidation products (MDA and CDs) and CPs was also revealed. SUEO attenuated 7b-OHC-induced cytotoxicity: 7b-OHC-induced cell death was reduced, GPx and SOD activities were normalized, and lower levels of MDA, CDs, and CPs were produced. Whereas a disturbed fatty acid profile was observed with 7b-OHC, similar fatty acid profiles were found in control cells and in cells cultured with 7b-OHC associated with SUEO. These data support the concept that this oil may have benefits in the prevention of neurodegenerative diseases.

1-B-41 *Bioenergtic control of synaptic plasticity by astrocytes during acute stress*

Ciaran Murphy-Royal[1], Andrew Boyce[1], Blanca Diaz-Castro[2], Baljit Khakh[2], Roger Thompson[1], Grant Gordon[1], Jaideep Bains[3]

[1]University of Calgary, [2]UCLA, [3]Hotchkiss Brain Institute

Astrocytes regulate synaptic transmission and plasticity at multiple levels including regulating synaptic energetics. Acute stress interferes with the ability of synapses to store information, however a direct role for astrocytes in this process has not been tested. As such we set out to investigate how acute stress impacts astrocytes and whether this underlies the stress-induced impairment in synaptic function. We used 2P microscopy and electrophysiology to reveal that acute stress impairs LTP in the cortex. Probing the mechanism, astrocyte-specific RNAseq highlighted genes associated with gap-junction channel expression. We investigated functional coupling by patching and filling astrocytes with fluorophores to assess dye flux in real-time. In

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naïve mice coupling was dynamic, responding to the metabolic demands of neurons. Following acute stress astrocyte coupling was impaired. To link stress-induced impairment in LTP with the effect of stress on coupling we targeted energy substrate delivery, as astrocyte metabolic networks sustain synaptic transmission and memory formation. Reducing L-lactate delivery from astrocytes to neurons impaired LTP, resembling stress. Conversely, supplementing astrocytes with L-lactate following stress recovered the stress-induced impairment in LTP. Importantly, blocking neuronal uptake of L-lactate impaired our ability to rescue synaptic plasticity. These data place astrocytes as central mediators of the stress response. Through modification in gap-junction coupling, astrocytes reduce energy availability limiting synaptic plasticity.

1-B-42 *The protein arginine methyltransferase PRMT8 regulates actin polymerization that is crucial for dendritic spine maturation and social behavior*

Hoi Ying Louisa Lo[1], Rui Dong[1], Quanwei Lyu[1], Kwok-On Lai[1]

[1]The University of Hong Kong

Most excitatory synapses are located in the dendritic spines. Mature mushroom-shaped spines are crucial for memory consolidation, while immature long and thin filopodia may serve as the precursors of dendritic spines. Spine maturation requires neuronal activity and mRNAs trafficking for local protein translation. However, the functions of many dendritically localized transcripts remain uncharacterized. Interestingly, these include mRNAs that encode protein arginine methyltransferases (PRMTs). PRMTs catalyze arginine methylation, a protein post-translational modification (PTM) in the nucleus that regulates gene transcription and splicing. Among the nine PRMTs, PRMT8 is unique because of its anchorage to the plasma membrane and its brain-specific expression (Lee et al., 2005). PRMT8 also possesses the interesting properties of acting as both methyltransferase and phospholipase D (Kim et al., 2015). Recent studies have unraveled the significance of PRMT8 in memory formation (Penney et al., 2017), but the underlying cellular mechanism remains unclear. Here we demonstrate that PRMT8 is enriched in dendritic spines. The prmt8 mRNA is present in dendrites and the expression of PRMT8 protein in hippocampal neuron depends on spontaneous neuronal activity. The function of PRMT8 in regulating excitatory synapse development is determined through shRNA-mediated knockdown as well as PRMT8 knockout mice. Our findings indicate that PRMT8-mediated arginine methylation is a novel regulatory PTM at the synapse that controls dendritic spine maturation and localization of excitatory synapses.

1-B-43 *Hydrogen peroxide evokes bursting in Aplysia bag cell neurons by gating a cation channel*

Alamjeet Chauhan[1], Neil Magoski[1]

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[1]Queen's University

Non-selective cation channels pass Na+, K+, and sometimes Ca2+, to elicit plateau potentials and persistent spiking in neurons responsible for learning, sensory processing, motor output, or neuroendocrine function. In the bag cell neurons of the marine snail, Aplysia, opening of a Ca2+-permeable, Ca2+-activated, voltage-dependent cation channel provokes a prolonged afterdischarge that initiates reproduction by releasing hormones into the blood. The afterdischarge is associated with the production of reactive oxygen species; as such, we tested if the effect of hydrogen peroxide (H2O2) on bag cell neurons is consistent with afterdischarge generation. Under whole-cell voltage-clamp, perfusion of micromolar to millimolar concentrations of H2O2 caused inward current in single cultured bag cell neurons. Preventing H2O2 reduction with mercaptosuccinate enhanced the current, while the reducing agent, dithiothreitol, lowered the response. In whole-cell current-clamp, H2O2 resulted in depolarization followed by a burst, similar to a genuine afterdischarge. The H2O2-evoked current was sensitive to the cation channel blockers, 9-phenanthrol or clotrimazole, as well as tetrodotoxin. Pretreatment with any of these blockers either attenuated the H2O2-induced firing or prevented bursting altogether. Finally, in desheathed bag cell neuron clusters, ex vivo sharp-electrode current-clamp recording showed that H2O2 evoked a bona fide afterdischarge, implying that H2O2 maybe crucial for reproductive behaviour by activating the non-selective cation channel that maintains the afterdischarge.

1-B-44 *Select divalent metals and verapamil block voltage-gated Ca2+ channels in Aplysia neuroendocrine cells*

David Wassef[1], Neil Magoski[1]

[1]Queen's University

Voltage gated Ca2+ channels are imperative for neuronal function, in that they pass electrical current and elevate intracellular Ca2+. The neuroendocrine bag cell neurons of the sea snail, Aplysia californica, control reproduction through the release of egg-laying hormone during a prolonged afterdischarge. This burst is initiated by acetylcholine gating an ionotropic receptor, resulting in depolarization and ~30 min of spiking. In this process, voltage-gated Ca2+ current presents a rapid component, that drives the upstroke of the action potential, and a persistent component, due to the channels cycling between the open and closed state with modest depolarization. We hypothesize that the acetylcholine-induced depolarization triggers bursting by recruiting persistent Ca2+ current. To target the Ca2+ current, we assayed various blockers on single cultured bag cell neurons using whole-cell voltage-clamp. The divalent metals, Ni2+ and Co2+, both inhibited the current with an IC50 of ~1 and ~1.5 mM, respectively, while the phenylalkylamine, verapamil, blocked with an IC50 of ~300 µM. However, while Cd2+ and the benzothiazepine, diltiazam, were effective, their presence was inevitably toxic to the cell. Future directions involve testing the impact of Ni2+, Co2+ or verapamil on the acetylcholine-evoked

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depolarization and changes to intracellular Ca2+ using whole-cell current-clamp with the Ca2+-sensitive dye, fura. Interaction between the ionotropic acetylcholine receptor and the voltage-gated Ca2+ channel may represent a common means to control neuroendocrine cell activity.

1-B-45 *Optogenetic induction of long-term potentiation at excitatory synapses onto hippocampal somatostatin interneurons*

Azam Asgarihafshejani[1], Isabel Laplante[1], Jean-Claude Lacaille[1]

[1]Université de Montréal

Hippocampal CA1 somatostatin interneurons (SOM-INs) are dendrite-projecting interneurons. Excitatory inputs from pyramidal cells onto SOM-INs show an mGluR1a-mediated form of long-term potentiation (LTP) which regulates metaplasticity of the CA1 circuit and hippocampal-dependent memory. In this study, we developed a protocol for optogenetic induction of LTP in SOM-INs in slices to use ultimately with in-vivo studies. For optogenetic activation of pyramidal cell excitatory inputs to SOM-INs, we injected AAV-CaMK2a-ChR2 (E123T/T159C)-mCherry in CA1 of SOM-Cre-eYFP mice. Whole-cell recordings showed that single optogenetic stimulation in oriens-alveus (Polygon; 5mW, 470nm) elicited EPSPs (EPSPopto) in SOM-INs in slices. Optogenetic theta burst stimulation (TBSopto; bursts of 4 pulses at 80Hz, repeated 5 times at 300 ms-1, given 3 times at 30 sec-1) produced LTP of EPSPopto. LTP was absent with low frequency TBSopto or in untetanized cells. LTP of EPSPopto was mediated by mGluR1a (blocked by LY367385) and mTORC1 (absent in conditional Rptor-/- mice). Optogenetically-induced SOM-IN LTP is thus analogous to electrically-evoked LTP. We found that TBSopto produced LTP of electrically-evoked EPSPs (EPSPelect) which was also mediated by mGluR1a and mTORC1. Finally TBSopto by whole field fiber illumination (300 µm diameter; Thorlabs) elicited similar LTP of EPSPopto. Thus, mGluR1a- and mTORC1- mediated LTP of CA1 pyramidal cell excitatory inputs onto SOM-INs is induced by optogenetic stimulation, providing a tool to examine the role of this plasticity in behaving animals.

1-B-46 *LTD requires engagement of two distinct mechanisms for suppression of CaMKII synaptic targeting*

Sarah Cook[1], Olivia Buonarati[1], Jonathan Tullis[1], K. Ulrich Bayer[1]

[1]UCD AMC

Learning, memory, and cognition are mediated by the long-term potentiation (LTP) and depression (LTD) of synaptic strength. These plastic processes require the Ca2+/calmodulin-dependent protein kinase II (CaMKII) and its auto-phosphorylation at T286. LTP requires CaMKII

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targeting to excitatory synapses, mediated by its binding to NMDA receptors. In contrast, during LTD, CaMKII instead targets inhibitory synapses. Once there, CaMKII promotes inhibitory potentiation, however, mechanisms directing LTD-induced CaMKII synaptic targeting are largely unknown. Here, we explore this differential CaMKII synaptic targeting and find that LTD requires suppression of CaMKII targeting to excitatory synapses by engagement of two distinct mechanisms: the death associated protein kinase 1 (DAPK1) and CaMKII T305/306 auto-phosphorylation (pT305/306). To study the regulation of CaMKII movement during plasticity, we used FingR intrabodies to simultaneously live-image endogenous CaMKII and markers for excitatory and inhibitory synapses in neurons from WT vs mutant mice. Either DAPK1 KO or a phospho-null mutation of CaMKII T305/306 was sufficient to allow accumulation of endogenous CaMKII at excitatory synapses not only after LTP but also LTD. Meanwhile, only pT305/306, but not DAPK1, was also required for the LTD-induced CaMKII accumulation at inhibitory synapses. Thus, both DAPK1 and pT305/306 regulate the bi-directional targeting of CaMKII during synaptic plasticity.

1-B-47 *The comprehensive analysis of ASIC-like subunits in Trichoplax adhaerens, an animal without a nervous system*

Wassim Elkhatib[1], Adriano Senatore[1]

[1]University of Toronto Mississauga

Trichoplax adhaerens is an early-diverging seawater animal with only six identified cell types that lacks a nervous system and synapses yet exhibits motile behavior. It feeds by gliding along surfaces, pausing upon detection of algae under its ventral epithelium, and feeding on it by external digestion. In a recent study, secreted peptides were shown to mitigate Trichoplax behavior, where ectopic application caused crinkling, turning and flattening and churning, most of which are associated with feeding. I seek to find the key ionotropic receptors responsible for this observed behaviour, by studying a group of ion channels known to respond to neuropeptides in other species called DEG/ENaC channels. Acid-sensing ion channels (ASIC) are part of this large family, and in humans, they are found in the nervous system where they play important roles in nociception, ischemic stroke detection and learning and memory. In early diverging animals such as Hydra, homologs of DEG/ENaC channels were found to potentially mediate neuromuscular transmission through peptide RF-amide signalling. Although Trichoplax has a repertoire of peptides that regulate behaviour, the receptors are still unknown. In our lab, we have cloned nine ASIC-like (TadASIC1-10) homologs from Trichoplax for functional expression in CHO-K1 cells. My work seeks to explore the gating mechanisms and the conformational dynamics of Trichoplax DEG/ENaC homologs, to further our understanding of this large group of ion channels and their roles in early metazoan physiology.

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1-B-48 *Electrical synapse location determines the strength of electrotonic transmission*

Jennifer Li[1], Neil Magoski[1]

[1]Queen's University

Neuronal communication is mediated by both chemical and electrical signalling, with the latter occurring via inter-cellular channels known as gap junctions. For the bag cell neurons of the marine snail, Aplysia californica, electrical coupling promotes synchronous firing during a prolonged afterdischarge of action potentials, which leads to the neuroendocrine release of reproductive hormone. In vivo, gap junctions are found between both bag cell neuron processes and/or somata. Thus, we tested if electrotonic transmission is influenced by the location of the gap junction by pairing bag cell neurons in culture followed by whole-cell voltage- or current-clamp. Pairs were separated based on the contact arrangement, either soma-soma or soma-axon/axon-axon. The junctional current in both groups showed weak voltage dependence; however, the junctional conductance was higher for soma-soma pairs vs soma-axon/axon-axon. Similarly, both the soma-soma coupling coefficient and the eletrotonic potential were larger, even though the pre- or postsynaptic input resistance did not differ between the two groups. Lastly, although the action potential threshold was the same regardless of arrangement, the propensity for presynaptic input to evoke a postsynaptic action potential was greater in soma-soma coupling. Thus, the strength of electrical transmission between bag cell neurons is dependent on their contact configuration. In vivo, synchronization may be facilitated by the appropriate localization of electrical synapses.

1-B-49 *The effect of neonicotinoids on identified electrically coupled cardiorespiratory neurons from the fresh water snail Lymnaea stagnalis.*

Eammon MacNeil[1], Neil Magoski[1]

[1]Queen's University

Neonicotinoids are agricultural pesticides, which act on nicotinic acetylcholine receptors to kill insects. The broad implementation of these products around the world exposes many non-target species to potentially lethal doses. For example, freshwater fish and molluscs are often affected in rural water reservoirs, causing major disruptions in the food web. The present study concerns the effect of two of the most widely used neonicotinoids, imidacloprid and clothianidin, on an electrically coupled two-neuron network in the CNS of the gastropod mollusc, Lymnaea stagnalis. The neurons in question, Visceral Dorsal 1 (VD1) and Right Parietal Dorsal 2 (RPD2), are large, readily identifiable, electrically coupled, and innervate the heart and mantle (primitive lung). As such, these cells are essential for animal survival; so much so, that there is an increase in mortality

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associated with a decrease in VD1-RPD2 coupling. Using dual sharp-electrode current-clamp recording from the isolated CNS, we show here that VD1 and RPD2 are excited in a concentration dependent fashion by the classical neurotransmitter acetylcholine. Furthermore, neonicotinoids cause both depolarization and attenuate the acetylcholine response. These data will form the basis for future testing of the effects of neonicotinoids on electrical coupling, either directly on gap junctions or indirectly through changes in cholinergic signalling. Overall, this work should provide further mechanistic insight into the environmental impact of neonicotinoids on freshwater organisms.

1-B-50 *The density and topography of interneuron subtypes in the claustrum*

Adarsh Badesha[1], Michelle Wang[1], Twinkle Joy[1], Brian Marriott[1], Jesse Jackson[1]

[1]University of Alberta

The claustrum is a hyper-connected forebrain nucleus sending and receiving connections with the entire neocortex. The majority of research on the claustrum has focused on its connectivity with cortical regions. However, the composition of local GABAergic interneurons remains incompletely understood. Here we describe the density and topography of claustrum interneuron subtypes across the rostro-caudal axis, relative to neighboring brain regions, and in relation to excitatory claustrocortical neurons projecting to the prefrontal cortex. We show that the claustrum contains a significantly greater number of cells containing neuropeptide Y (NPY) and somatostatin (SST) relative to parvalbumin (PV). SST and NPY staining in the claustrum and endopiriform cortex was greater than neighboring insula, piriform, striatum, and somatosensory cortex, whereas parvalbumin levels were relatively reduced in the claustrum. SST, NPY, and PV interneurons differed in their rostro-caudal organization, and their proximity to claustrocortical projection neurons. These data suggest different claustrocortical projection neurons may be controlled by different ratios of PV, SST, and NPY mediated inhibition.

1-B-51 *Altered dopaminergic modulation of basal glutamatergic transmission in ACC of mice with chronic pain*

soroush Darvish-Ghane[1], Loren Martin[2]

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

The desire for a rewarding experience and avoiding a painful experience are unified in opposition. Dopamine (DA), as the neurotransmitter to signal the anticipation of a reward can inhibit anterior cingulate cortex (ACC) basal glutamatergic transmission mediated by AMPA receptors (AMPAR). This form of glutamate mediated transmission in the ACC is responsible for the unpleasant

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sensation of pain and development of chronic pain. By using patch-clamp technique, we show that administration of DA to brain slices inhibits AMPAR mediated currents in ACC pyramidal neurons. This inhibition is PKA-independent and is primary mediated by D2- receptor class of DA-receptors. Surprisingly we uncover that D1R class of receptor agonists possess off target binding properties in the ACC with robust neuromodulatory properties that may indicate for a novel co-signalling of serotonin and dopaminergic receptors in the ACC. Meanwhile, an inflammatory model of chronic pain was established by injection of complete freund's adjuvant (CFA) in both hindpaws of adult mice. These mice displayed hyperexcitability of the glutamatergic transmission in the ACC with a primarily pre-synaptic component. Interestingly, modulation of glutamatergic transmission by DA was significantly lost after four days of experiencing chronic inflammatory pain. Our results are first to indicate a change in dopaminergic circuitry in a cortical region selective for integration of pain.

1-B-52 *Inhibition of ATGL reduces inflammation in LPS-activated microglial cells*

Arturo Machuca-Parra[1], Demetra Rodaros[1], Romane Manceau[1], Cyril Laurent[1], Nathalie Arbour[1], Stephanie Fulton[1], Thierry Alquier[1]

[1]CRCHUM - Université de Montréal

Microglia is the primary cell population responding to insults that alter brain homeostasis generating the M1 and M2-type profiles. During inflammation, lipid droplets (LDs) are formed and constitute sites for the synthesis and storage of inflammatory mediators in many cells, including microglia. Specific glycerolipid lipases surrounding LDs catalyze the hydrolysis of triglycerides (TG). The Adipose Triglyceride Lipase (ATGL) participates in the hydrolysis of TG and contributes in lipid homeostasis by regulating glycerolipid metabolism in several cells. However, the role of ATGL and LDs in microglial function and neuroinflammation is unknown. We found that ATGL is enriched in FACS-purified microglia from adult mice and postnatal microglial cells in cultures. Primary microglial cells derived from P2 mice were treated with Atglistatin (a specific ATGL inhibitor). A significant decrease in apoptosis ($p<0.0002$), cytotoxicity ($p<0.0004$) and LDs with Atglistatin was observed. ATGL expression was decreased ($p<0.001$) with LPS. Expression levels of IL-6 ($p<0.0001$) and MCP-1 ($p<0.0001$) were decreased with Atglistatin and LPS. With ORlistat, a general lipase inhibitor, expression levels of IL-1beta ($p<0.0001$), IL-6 ($p<0.0001$), and NF-kappaB ($p<0.0001$) were significantly decreased. Interestingly, a significant increase ($p<0.005$) of TG content in microglia treated with Atglistatin and LPS was observed. We propose that ATGL regulates inflammatory responses in LPS-stimulated microglia, suggesting a role of ATGL during inflammation in vitro.

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1-B-53 *Connexin-36 (Cx36) interaction with calmodulin kinase II (CaMKII) is modulated by ionotropic NMDA receptors and the pannexin-1 channel*

Ryan Siu[1], Cherie Brown[1], Christiane Zoidl[1], David Spray[2], Georg Zoidl[1]

[1]York University, [2]Albert Einstein College of Medicine

The synergistic actions of calcium, calmodulin (CaM), and calmodulin kinase II (CaMKII) constitute a central mechanism for synaptic plasticity of chemical synapses. Our research has shown previously that connexin-36 (Cx36) uses CaM/CaMKII interaction in a similar Ca2+-dependent process for plasticity of electrical synapses. Here, we hypothesized that beyond utilizing similar molecular machinery, both types of synapses communicate efficiently. To investigate a potential cross-communication between the two types of synapses, we used pharmacological interventions and TALEN knockout Neuro2a cells with ablation of the NMDAR subunit NR2b or the Panx1 channel. State-of-the-art imaging techniques including Fluorescence Resonance Energy Transfer (FRET), functional dye uptake after photobleaching (gapFRAP), and Arclight fluorescence quantification, were used to analyzed both temporal and spatial dimensions of Cx36 interaction with CaMKII at single cell resolution. Pharmacological interventions modeled modes of neural activities. Outcomes demonstrate that 1) NMDA receptor or Pannexin-1 (Panx1) channel antagonists, or 2) TALEN knockout of either NMDA receptor subunit NR2B, or the Panx1 channel in vitro efficiently reduced CaMKII interaction with Cx36, in effect closing Cx36 gap junction channels. Current results support that cross-communication between the two types of synapses exists, and that both NMDA receptors and Panx1, each on its own modulate plasticity of electrical synapses containing Cx36.

1-B-54 *Auxiliary proteins target distinct regions on AMPARs to modulate receptor function*

Amanda Perozzo[1], Marika Arsenault[1], Mark Aurousseau[1], Derek Bowie[1]

[1]McGill University

AMPA receptors (AMPARs), a family of ligand gated ion channels, are fundamental for synaptic transmission across all brain regions. Recent work has identified that the AMPAR pore forming subunits co-assemble with a variety of auxiliary proteins. Proteomic analysis suggests that AMPAR signaling complexes are made up of at least 3 families of transmembrane proteins, namely the claudin family of proteins including TARPs and GSG1L, the cornichon homologs (CNIHs) and the CKAMP family. These accessory proteins are garnering much interest as they have been shown to not only regulate the trafficking of receptors into and out of the synapse, but also directly affect their functional behaviour. However, the underlying structural basis for auxiliary protein modulation of AMPARs is poorly characterized. We have identified a hotspot on the AMPAR ligand-binding domain (LBD) that governs auxiliary protein interactions with AMPARs. Our data

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show that the electropositive KGK motif, a conserved extracellular domain previously identified by our lab, interacts exclusively with Type I and Type II TARPs, as well as GSG1L. In contrast, an electronegative region on AMPARs is implicated in CNIH-3 modulation of the receptor. CKAMP44 is unaffected by mutation of either of these regions, suggesting that this protein exerts its effects via other sites on the channel. In summary, this work establishes that auxiliary proteins modulate AMPARs by targeting distinct structural binding sites, which confers unique gating properties and physiological identities to individual neuronal populations in the CNS.

1-B-55 *Synaptic mechanisms underlying the network state-dependent recruitment of the interneuron-specific interneurons in the mouse CA1 hippocampus*

Xiao Luo[1], Alexandre Guet-McCreight[2], Vincent Villette[1], Ruggiero Francavilla[1], Simon Chamberland[3], Frances Skinner[4], Lisa Topolnik[1]

[1]Neuroscience Axis, CHU de Québec Research Center (CHUL), [2]Krembil research Institute, University Health Network, [3]New York University, [4]Krembil Research Institute

In the hippocampus, a highly specialized population of interneuron-specific (IS) inhibitory cells coordinates the activity of local inhibitory circuits. While disinhibition is thought to play a role in hippocampal learning, the contribution of IS cells to network activity remains unclear. Here we reveal the synaptic properties of CA1 type 3 vasoactive intestinal peptide/calretinin co-expressing IS (IS3) cells and demonstrate their recruitment during network states in awake mice. Using patch-clamp recordings and two-photon glutamate uncaging, we found that IS3 cells fire spikes in response to repetitive or spatially clustered excitatory inputs. In particular, both the Schaffer collateral and the temporoammonic pathways could drive IS3 cell firing in vitro. Using an in vivo-like computational model of an IS3 cell, we predicted that these inputs could drive IS3 cells to spike rhythmically during theta rhythms, as well as transiently during sharp-wave ripples (SWR). Furthermore, two-photon calcium imaging in awake mice revealed a range of IS3 activities across the behavioral states. As a rule, somatic calcium transient (CaT) events were delayed relative to locomotion. Moreover, analysis of the CaT onset time during theta-run episodes suggested preferential firing of IS3s around the rising/peak phases of theta waves. In addition, significant CaTs were detected during immobility but not coupled to SWRs. Thus, while synaptic properties of IS3 cells are predicted to generate a particular output, additional factors may modulate their recruitment during behavioral and network states.

1-B-56 *Characterization of Vip interneuron plasticity in the motor cortex*

Amanda McFarlan[1], Chaim Weinerman[1], Maria Haddad[1], Jesper Sjöström[1]

[1]McGill University

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Most anti-epileptic drugs act via GABAergic inhibitory neurons (INs), including Martinotti cells (MCs), to impact local activity. There are many IN types, of which vasoactive intestinal peptide-expressing (Vip) INs are particularly poorly described, e.g. nothing is known about Vip IN synaptic plasticity. Yet, Vip INs have a key disinhibitory role by inhibiting nearby INs which increases seizure susceptibility and duration. Vip INs thus constitute a promising seizure control point. We therefore set out to characterize mouse motor cortex Vip INs and their plasticity. We bred transgenic mice expressing Channelrhodopsin-2 (ChR2) in Vip INs by crossing Vip-Cre and ChR2 reporter mice (Ai32-flox). Using 2-photon imaging, we targeted Vip INs for whole-cell recording in acute slices and measured their electrophysiological properties. Vip IN density across cortical layers was assessed by immunohistology. Vip IN spike threshold varied with cortical depth (layer 2/3: -40.3 ± 1. 6 mV, n=30 cells vs layer 5: -34.1 ± 2.0 mV, n=14, $p < 0.05$) with a consistently low rheobase current (73 ± 10 pA; n=44). Spike half width and height were 0.95 ± 0.04 ms and 44.0 ± 2.0 mV (n=44). Vip INs most densely populated L2/3 (52% ± 2%; n=7 animals), followed by L5 (24% ± 2%), L6 (17% ± 1%), L1 (3.4% ± 1%) and L4 (3.6% ± 1%, $p<0.001$). We are currently characterizing the plasticity of Vip IN connections onto MCs, with preliminary data suggesting anti-Hebbian LTD arising from a repeated pattern of coincident firing. In conclusion, Vip IN plasticity may be possible to harness for alleviating epilepsy.

1-B-57 *Investigating oligodendrocyte precursor cell niche differences in the neocortex*

Daniel Dennis[1], David Kaplan[2], Freda Miller[2]

[1]SickKids Research Institute, [2]The Hospital for Sick Children

Demyelinating diseases such as multiple sclerosis result in reduced signal conduction in nerves due to damage to the myelin sheath and loss of oligodendrocytes. Oligodendrocytes, the myelinating glial cells of the CNS, are generated throughout life by oligodendrocyte progenitor cells (OPCs) which are present in both gray and white matter of the mammalian brain. OPCs are distributed throughout the CNS and represent a system that may be manipulated for endogenous repair of damaged myelin. How OPCs are induced to proliferate and differentiate by growth factors in their environment has not been investigated at a systems level. In addition, OPCs do not have a uniform behaviour. OPCs respond differently to growth factors based on whether they reside in gray or white matter regions. These differences in behaviours of gray and white matter OPCs imply a niche-based heterogeneity and thus a difference in the readiness of these OPCs to be involved in myelination and myelin repair. Using a combination of RNA-Seq and scRNA-Seq, we investigate the differences in gray and white matter niches and construct a signaling network that may influence OPC behavior in those niches. To model OPC niche differences we have identified a cortical ligand environment and determined the receptors expressed in OPCs in adult mouse cortices.

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1-B-58 *Information processing at hippocampal mossy fibers through target-cell specific plasticity*

Julian Rossbroich[1], Maxime Houtekamer[1], Richard Naud[2], Katalin Tóth[1]

[1]CERVO Brain Research Centre, Université Laval, [2]Centre for Neural Dynamics, University of Ottawa

Synaptic connections from dentate granule cells (GC) to CA3 in the hippocampus are crucial for memory specificity and spatial navigation. GCs fire preferentially in high-frequency bursts, and their axons, called mossy fibers (MF), target both pyramidal cells and feed-forward inhibitory interneurons. We study the target-cell specific dynamics of synaptic transmission at MF synapses to understand information transfer during GC bursts. Specifically, GC output converges in CA3 after undergoing three distinct transformations: Using electrophysiological recordings, we previously revealed that MF-pyramidal cell synapses transmit information by effectively counting the number of spikes (AP counting). Our new results suggest that spike transmission at MF-interneuron synapses is heterogenous and can be classified into (1) rate coding synapses and (2) frequency independent synapses. To study how these excitatory and feed-forward inhibitory input streams converge in CA3, we are developing a computational framework, restricted by experimental data. Our newly developed phenomenological model of short term facilitation describes the unique dynamics of AP counting in response to burst firing, which could not be captured with traditional synapse models. We are currently integrating the new facilitation model with spiking neuron models to construct a small-scale network simulation. This model enables investigations of how granule cells coordinate activity and plasticity at the network level.

1-B-59 *TNF Dependent synaptic and behavioral modifications in response to acute stress*

Gina Kemp[1], Haider Altimimi[1], David Stellwagen[1]

[1]McGill University

Understanding the neuroscience of stress-related disorders is important for developing effective therapeutic options. One hallmark of the acute stress response is the potentiation of the hippocampal excitatory synapses and is associated with an increase in anxiety-like behaviour. Tumor necrosis factor (TNF) is an inflammatory cytokine involved in inverse regulation of neuronal AMPA and GABA receptors, favoring an overall excitatory output. Given this, we hypothesize that TNF is involved in this synaptic potentiation and the resulting behavioral manifestations of stress. Using a mouse model, we employed genetic and pharmacological tools to study the effects of TNF on the stress response, behaviorally, biochemically and synaptically. We found that stress is

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correlated with an elevation in TNF levels. Blocking TNF signaling prevented the stress-induced synaptic and behavioural phenotypes. Housing conditions were also found to interfere with both TNF levels and the behavioral stress-response; group housing animals post-stress confer a state of resilience that is lacking in singly housed animals. We conclude that TNF is a necessary downstream signal for the synaptic and behavioral manifestations of the stress-response in mice.

1-B-60 *In vivo two photon imaging of stroke related changes in connectivity and functional activity of vip dis-inhibitory interneurons*

Mohammad Motaharinia[1], Kimberly Gerrow, Emily White[1], Nuo Liang, Craig Brown[1]

[1]Division of Medical Sciences, University of Victoria, Victoria, BC

Although inhibitory cortical interneurons play a critical role in regulating brain excitability and function, the effects of stroke on these neurons is poorly understood. In particular, interneurons expressing vasoactive intestinal peptide (VIP) specialize in inhibiting other classes of inhibitory neurons, and thus serve to modulate cortical sensory processing. To understand how stroke affects this circuit, we imaged VIP neuron structure and function (using GCaMP6s) before and after focal stroke in forelimb somatosensory cortex. Stroke led to a significant loss of peri-infarct pre-synaptic boutons and dendritic spines that was followed by a wave of bouton/spine production. Functionally, the fraction of forelimb responsive VIP interneurons and their response fidelity was significantly reduced in the first week after stroke. The loss of responsiveness was most evident in highly active VIP neurons, whereas less active neurons were minimally affected. Additionally, the variance in response fidelity after stroke was comparatively high and therefore less predictable than that observed before stroke. These findings reveal the dynamic and resilient nature of VIP neurons and suggest that a sub-population of these cells are more apt to lose sensory responsiveness during the initial phase of stroke, whereas some minimally responsive cells are progressively recruited into the forelimb sensory circuit. Furthermore, stroke appears to disrupt the predictability of sensory evoked responses in these cortical interneurons which could have important consequences for sensory perception.

C - Disorders of the nervous system

1-C-61 *Bidirectional amelioration of mnemonic deficits by the lysine acetyltransferase CBP/p330-associated factor in the 3xTG mouse model of Alzheimer's disease*

Samantha Creighton[1], Alexa Desimone[1], Kristen Jardine[1], Megan Zmetana[1], Sabrina Castellano[2], Ciro Milite[2], Gianluca Sbardella[2], Boyer Winters[1]

[1]University of Guelph, [2]University of Salerno

The acetylation of histone and non-histone proteins by lysine acetyltransferases (KATs) supports many mnemonic processes. As there is growing evidence that dysregulation of acetylation plays

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a role in cognitive deficits and neuropathology in Alzheimer's disease (AD), increasing KAT activity has emerged as a promising therapeutic strategy. However, acetylation patterns in AD are likely multifarious and deficits may not always be ameliorated by activating KATs. Indeed, while PCAF activation enhances memory in normal rodents, in AB-treated rats, PCAF inhibition attenuates AD-like cognitive deficits, suggesting that PCAF activity can be detrimental. By longitudinally evaluating the effects of acute PCAF activation and inhibition on object recognition (OR) memory at 3, 6, 9, and 12 months of age, we show that PCAF bidirectionally regulates cognition in male and female triple transgenic (3xTG) AD mice. At 3 and 6 months of age, prior to the development of OR deficits, the PCAF activator, SPV-106, enhanced short- (5min) and long-term (3h) OR, whereas the PCAF inhibitor, embelin, impaired. At 9 months of age, when OR impairment was first observed, SPV-106 ameliorated the long-term OR deficit. At 12 months of age, however, SPV-106 induced a short-term OR impairment, while embelin ameliorated the long-term OR deficit. A similar, albeit accelerated, pattern of results was observed for spatial memory. Our behavioural findings reveal a unique and complex role for PCAF in the progression of AD. We are currently investigating the epigenetic and pathological correlates of these effects.

1-C-62 *A gene network affected by betamethasone in non-human primates translated to humans interacts with adversity conditions influencing anxiety response in healthy girls*

Danusa Mar Arcego[1], Nick O'Toole[1], Jan-Paul Buschdorf[2], Nirmala Arul Rayan[3], Irina Pokhvisneva[1], Carla Dalmaz[4], Barbara Barth[1], Euclides de Mendonça Filho[4], Patricia Pelufo Silveira[1], Michael Meaney[1]

[1]McGill University, [2]Singapore Institute for Clinical Genetics, [3]Genome Institute of Singapore, [4]Universidade Federal do Rio Grande do Sul

Exposure to stress has consistently been associated with the development of emotional disorders, however, the precise role of stress released glucocorticoids remains unclear in this context. Our aim was to use animal data to create a biologically relevant polygenic score and investigate its interaction with environmental stressors in the development of anxiety in a child community-based birth cohort (MAVAN, evaluated at 6 years of age). We used RNA-sequencing data from posterior dentate gyrus (pGD) of adult female Macaca fascicularis after chronic Betamethasone (glucocorticoid) or saline injections for 8 consecutive days in two cohorts: Vietnam and Singapore (N=6/group each cohort). Enrichment analysis showed that upregulated genes by betamethasone compared to saline are involved in apoptosis, while downregulated genes are involved in immune response, cell-matrix interactions and proteolysis (FDR<0.05, Metacore®). A common gene list comparing the cohorts was used to create an expression-based polygenic risk score (ePRS),

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weighing each SNP by the slope of gene expression (GTex). Linear regression analysis showed a significant interaction between ePRS and environmental adversity for the Koala task (measures anxiety and fear levels, ß=0.44; P=0.02), in which the high expression group varied in anxiety levels according to the exposure to adversity. Variations in the expression of the gene network associated with response to betamethasone in the pDG of macaques predict resilience or susceptibility to adversity on the development of anxiety in a community sample of girls.

1-C-63 *Cognitive impairment in Parkinson's disease is captured by personalized Virtual Brain models*

Kelly Shen[1], Zheng Wang[1], Tanya Brown[1], Anthony McIntosh[1]

[1]Baycrest

Although Parkinson's disease (PD) is initially characterized by motor symptoms, >80% of patients develop dementia over the course of the disease. Using static neuroimaging profiles alone to develop biomarkers for PD-dementia is challenging because affected brain networks are also implicated in other dementias. Moreover, disease mechanisms occur at cellular/molecular scales and are undetectable with current noninvasive neuroimaging tools. We begin to address these challenges by integrating neuroimaging data with underlying cellular mechanisms via large-scale dynamic network models using TheVirtualBrain (TVB) simulation platform. Personalized models of PD (N=70), prodromal forms of PD (N=13) and healthy controls (N=19) were created in TVB using each individual's structural connectome. The local dynamics of each brain region was modeled using a mean field model of coupled excitatory and inhibitory populations. Model parameters (global coupling, noise, & local coupling) were varied to optimize the fit between empirical and simulated resting-state functional connectivity. Good fits were obtained for all subject groups (mean: 0.38; range: 0.26-0.49). A multivariate analysis showed that increased global coupling and lower noise were related to better cognitive scores ($p < 0.01$). These findings suggest that disruptions to long-distance integration underlies cognitive impairment in PD. Our models are a solid first step towards the deliberate integration of neuroimaging data with computational modeling to elucidate the biophysical substrates of disease mechanisms in dementia.

1-C-64 *Cellular senescence in dopamine neurons*

Benjamin Kolisnyk[1], Markus Riessland[1], Tae Wan Kim[2], Jordan Pearson[1], Emily Park[1], Lorenz Studer[2], Paul Greengard[1]

[1]The Rockefeller University, [2]Memorial Sloan Kettering Cancer Center

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Cellular senescence is a mechanism used by mitotic cells to prevent uncontrolled cell division. As senescent cells persist in tissues, they cause local inflammation and are harmful to surrounding cells, contributing to aging. The contribution of cellular senescence to neurodegeneration is still unclear. SATB1 is a DNA binding protein associated with Parkinson's disease. We find that SATB1 plays an active role, repressing cellular senescence in post-mitotic dopaminergic neurons. Loss of SATB1 causes activation of a cellular senescence transcriptional program in dopamine neurons, both in human stem cell-derived dopaminergic neurons and in mice. We observed phenotypes which are central to cellular senescence in SATB1 knockout dopamine neurons in vitro and in vivo. Moreover, we found that SATB1 directly represses expression of the pro-senescence factor, p21, in dopaminergic neurons. Finally, we find demonstrate that loss of SATB1 from dopamine neurons in vivo produces local inflammation and active removal of the dopamine neurons by microglia. Our data implicate senescence of dopamine neurons as a contributing factor to the pathology of Parkinson's disease.

1-C-65 *Diffusion imaging fiber tractography: Prosopagnosia and automatic facial expression analysis defy in progressive Alzheimer's*

Christina Vadiyala[1], Ganesh Elumalai[1], Ashleigh haughton[1], Tajnin Bint Mohammed Hashim[2]

[1]Team NeurON - Texila American University, [2]Texila American University

INTRODUCTION: Prosopagnosia is a common sign in Alzheimer's Disease(AD), especially characterised with loss of familiar face recognition and processing of facial expression. The invariant aspects of the face are analysed by Fusiform Face Area(FFA), located in the lateral fusiform gyrus and variant aspects like eye gaze, expression, lip movements facilitating social communication are analysed in Superior Temporal Sulcus(STS). In Alzheimer's patients, atrophy of FFA and STS are claimed to be cause of prosopagnosia and failure of facial expression analysis. We used seventy-two Diffusion Tensor Imaging(DTI)datasets(36 Males and 36 Females), between the age ranges from 60-120 years. Study aimed to identify and analyse the neural structural connectivity in failure of familiar face recognition and processing of facial expressions in Alzheimer's Patients, using "Diffusion Imaging fiber Tractography". RESULTS: Tractography reveals the highest number of fibers are in females than males, in both control and AD cohort. The tract from visual cortex to the Fusiform Gyrus show increased number of fibers for males in AD and females in progressing stages of AD. In both males and females, the tract from visual cortex to the STS revealed highest number of fibers in progressing stages and plunged deterioration in AD. The results are significant at $p<0.001$. CONCLUSION: Prosopagnosia in Alzheimer's is due to the decreased nerve fibers to the FFA as believed. Failure of facial expressions analysis are not only concerned with cognitive deficit, but it also involves cortical tract deterioration.

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1-C-66 *rhyme and rhythm of music in epilepsy*

Marjan Rafiee[1], Dorsa Zabihipour[1], Danielle Andrade[2], Eduard Bercovici[3], Esther Bui[2], Jose del Campo[3], Peter Carlen[1], Peter Tai[2], Richard Wennberg[2], Taufik Valiante[4]

[1]Krembil Research Institute, [2]Krembil Research Institute | Division of Neurology, Department of Medicine, University of Toronto, [3]University of Toronto, [4]Krembil research Institute, University Health Network

Rational-Epilepsy is among the most common neurological diseases. Many individuals continue to have seizures despite medical and surgical treatments, suggesting alternate management strategies are required. We explored the therapeutic benefits of listening to a specific musical piece (Mozart K448), which has demonstrated promise over the last 20 years. Methods-Using a randomized controlled crossover design, individuals with epilepsy were randomly assigned to either start the intervention by listening to Mozart, or a phase scrambled control piece in three months intervals over a one year study period. Seizure diary entries were obtained, next to electroencephalographic (EEG) recordings. Results-Our results revealed a reduction in seizure counts during three months of listening to Mozart (-40 ± 10 %), with an increase of 13 ± 11 % for the control piece (n = 14). The non-parametric Mann-Whitney U test revealed a treatment effect in an intention to treat analysis: significant differences existed in seizure counts between the period of listening to Mozart versus the control piece (p-value=0.012, p-value < 0.05 was considered as significant), with one individual becoming seizure-free during the treatment period. Statistical analysis revealed both a period effect and a potential carry-over effect after the treatment period. Conclusions - Our results demonstrate the promising effects of listening to Mozart K448 on reducing seizure counts. Using a spectrally similar control piece, our study contrasts with previous reports that were limited by a "no music" control condition.

1-C-67 *Neural structural connectivity analysis of olfactory saccadic attention deficit in Alzheimer's patients*

Nadira Sewram[1], Ganesh Elumalai[2], Panchanan Maiti[3], Harshita Chatterjee[1], Nitya Akarsha Surya Venkata Ghanta[2], Nneoma Somtochukwu Osakwe[1]

[1]Texila American University, [2]Team NeurON - Texila American University, [3]Saginaw Valley State University, MI, USA

Olfactory deficits are mostly seen in early mild cognitively impaired (MCI) patients and in early Alzheimer's disease (AD). Like in most neurodegenerative disorders, olfactory dysfunction is a clinical marker appearing years before the declining motor and cognitive functions in AD. A study comparing the association of odour stimuli with visual response between a control group and AD-affected group concluded stating degeneration in the central olfactory areas as the cause, but the specific structure involved remained unknown. Identification of this structure could serve as a

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potential clinical marker for AD severity and help monitor disease progression. This study includes Diffusion tensor images (DTI) datasets of 72 control and 72 Alzheimer patients from both the sexes, with ages ranging from 55 to 120 years. The aim of this study was to identify the structure, variation in which gives rise to Olfactory Attention Deficit by identifying the structural connectivity between the Olfactory Cortex and Frontal Eye Field, using DTI fibre tractography to establish Olfactory - Saccadic pathway. It also focuses on comparative analysis of the tracts in progressing stages of AD and hemispheric dominance in all stages. Progressive changes were seen from MCI to Mild AD in both sexes, also a bimodal distribution of fibres was seen in both sexes, but this distribution was mostly seen in females than in males. The mostly affected hemisphere in all the experimental stages is right. Therefore, any variational changes to right of the brain may cause complete olfactory attention deficit.

1-C-68 *Tactile stimulation improves cognition & motor skills in Alzheimer's disease model mice*

Shakhawat Hossain[1], Hadil Karem[2], Zahra Jafari[2], Majid Mohajerani[2], Bryan Kolb[2]

[1]CCBN, University of Lethbridge, [2]Lethbridge University

Alzheimer's disease (AD) is a neurodegenerative brain disorder that causes deficit in cognition, motor coordination, emotional, and social behaviour. These symptoms are correlated with reduced neuronal complexity, increased deposition of plaques and tangles in brain, abnormality in neurotransmitters, and shrinkage of brain regions. In this research, we focused on an intervention called tactile stimulation (TS) to encounter the early onset of AD to slow or halt the development AD. Numerous research has shown that TS increases the FGF-2, acetylcholine, and astrocytes in the brain. In addition, TS improves cognition and motor coordination in premature and institutionalized infants, slows the progression of AIDS by improving the immune system, and treats hypertension, anxiety, and wound healing from burns. To conduct this study, we applied TS on APPNL-G-F mice from both sex at 4 months and employed a combination of behavioral and histochemical analysis to investigate the benefit of TS on the development of AD. The impact of TS on cognitive and motor tasks and development of beta amyloid plaques (Aβ) were measured at 6 months. The results from behavioural tests revealed that TS improved both cognition and motor coordination in APPNL-G-F mice and these findings were correlated with reduced amount of plaques formation in associated brain regions.

1-C-69 *Metabolism and turnover of amyloid-β peptides*

Irem Ulku[1], Gerhard Multhaup[1]

[1]McGill University

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One of the pathological hallmarks of Alzheimer's Disease is amyloid plaques, which are mainly composed of amyloid β (Aβ) peptides. Aβ peptides of varying lengths are generated by sequential cleavage of amyloid precursor protein, first by β-secretase (BACE1) followed by γ-secretase. Longer Aβ species (e.g. Aβ40 and Aβ42) can then further undergo amyloidolytic processing, a normal process of degradation that has remained poorly understood. Recently, we found that BACE1-catalyzed cleavage of Aβ40 and Aβ42 results in the production of a non-amyloidogenic metastable intermediate, i.e. Aβ34. Unlike Aβ40 and Aβ42, Aβ34 is non-toxic and non-aggregating. Presently, we investigated where and how Aβ34 is generated in the cell and what role the γ-secretase complex may play in this process. The γ-secretase complex has four subunits, including the catalytic subunit Presenilin (PS) 1 or 2. Although both PS1- and PS2-γ-secreatases possess overlapping enzymatic properties, they have distinct influence on Aβ abundance. PS2 selectively cleaves substrates in late endosome/lysosome and generates intracellular Aβ pool, whereas PS1 selectively cleaves substrates on the cell surface. Endosomal compartments, such as late endosomes, provide an acidic environment that is crucial for BACE1 activity and offer optimal conditions for the BACE1-mediated degradation of PS2-derived Aβ substrates. Our preliminary data from genetic approaches, including siRNA knockdown of PS1/2 in BACE1 overexpressing SH-SY5Y cells, suggest that BACE1 generates Aβ34 in intracellular compartments from PS2-derived Aβ species.

1-C-70 *Clusterin-amyloid interactions and their role in Alzheimer's disease pathology*

James Eng[1], Gerhard Multhaup[1]

[1]McGill University

A critical event in the pathogenesis of Alzheimer's disease (AD) is the accumulation of amyloid-beta (Aβ) peptides into toxic Aβ oligomers in the brain causing neuronal damage and synaptic loss. Clusterin is an extracellular chaperone protein linked to sporadic AD through genome-wide association studies and clusterin has been previously shown to interact directly with Aβ peptides and modulate their aggregation behavior in vitro. While clusterin is capable of directly binding to Aβ peptides, the mechanism and biological functions of clusterin-Aβ interactions have remained unclear. The present study investigates clusterin-Aβ interactions and the influence of clusterin on Aβ peptide abundance. Preliminary data has identified that, in the presence of clusterin, there was an increase in Aβ40 in conditioned cell medium, whereas the levels of Aβ42 and Aβ34 showed no change. When clusterin and APP were expressed at different ratios, higher levels of Aβ40 were seen when the clusterin to APP ratio was the highest; however, no changes in Aβ42 or Aβ34 levels were observed. These data suggest that clusterin preferentially affects Aβ40 levels over Aβ42 or Aβ34. We are currently testing two hypothesis, (i) Increased Aβ40 levels compared to control may be a result of clusterin binding to Aβ40¬ preferentially and preventing its degradation by forming

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a stable complex, or (ii) clusterin affects APP processing by the γ-secretase complex which results in an increase of Aβ40 production over other Aβ species.

1-C-71 *Antidepressant doses of ketamine restore hippocampal LTP and long-term spatial memory in the Wistar-Kyoto model of depression*

Lily Aleksandrova[1], Yu Tian Wang[1], Anthony Phillips[1]

[1]University of British Columbia

Accumulating evidence implicates dysfunction within the glutamatergic system and dysregulation of synaptic plasticity, particularly in the hippocampus (HPC), in the pathophysiology of depression. Here we utilized the Wistar-Kyoto (WKY) model of endogenous stress susceptibility and depression, which exhibits behavioural, neurochemical and endocrine parallels to clinical depression. We found that in addition to a depressive-like phenotype in various preclinical tests, WKYs have impaired hippocampal CA1 long-term potentiation (LTP) in vivo, which is associated with accelerated forgetting of long-term spatial memories in the object location recognition (OLR) task. Importantly, a single systemic injection of ketamine (5mg/kg, ip), which produced rapid and sustained antidepressant effects in the forced swim test (FST), also acutely restored the impaired LTP, led to a sustained increase in hippocampal AMPAR-mediated neurotransmission and fully rescued the long-term spatial memory deficit in WKYs. Interestingly, the ketamine metabolite (2R,6R)-HNK also restored CA1 LTP and OLR performance, but failed to increase immobility in the FST, giving rise to a dissociation between rescuing LTP and antidepressant effects in the FST in these rats. Based on these findings, we propose that, at least in the WKY model of depression, restoring dorsal HPC LTP does not seem to underlie ketamine's "canonical" antidepressant effects, but may instead mediate reversal of hippocampal-dependent cognitive deficits, including long-term spatial memory that are also key features of clinical depression.

1-C-72 *Associative Visual Object Agnosia (AVOA): Neural-Cortical connectivity analysis in progression stages of Alzheimer's disease*

Divya Singh[1], Ganesh Elumalai[2], Panchanan Maiti[3], Nitisha Tricia Dyal[1], Geethanjali Vinodhanand[2], Valencia Lasandra Camoya Brown[1], Venkata Hari Krishna Kurra[1], Nitya Akarsha Surya Venkata Ghanta[2]

[1]Texila American University, [2]Team NeurON - Texila American University, [3]Saginaw Valley State University, MI, USA

INTRODUCTION: Visual agnosia is a promptly noticed neurological deficit in Alzheimer's disease (AD), affects the inferior temporal lobe, which leads an inability to perceive objects. The

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interconnection between the two cortices in visual ventral stream, the visual cortex (BA 17, 18, 19) and inferior temporal lobe (BA 20) explain how we perceive and recognize the objects, called associative object visual perception. We Team NeurON, focused on correlating the neural structural connectivity with associative visual agnosia in Alzheimer's patients using "Diffusion Tensor Imaging Tractography". The study involves fifty DTI datasets, both the sexes of Control and disease progression stages of AD, with age ranges from 50 to 90 years. RESULTS: On observation, the females displayed with progressive increase in the (number and volume) fibers among the cognitive declining stages of AD. But, the males, noticed with a bi-modal variations (number and volume) of fibers, within the disease progression stages of AD. CONCLUSION: Although the statistical analysis was insignificant, it was noticed that the males are predominantly affected than females. The current observations, propose an insight to understand the bi-modal distribution of fibers in the male and progressive increase of fibers in the female, from the control to disease progression stages of AD. However, these findings need to be confirmed with functional and effective connectivity analysis for further understandings. Keywords: Ventral or What stream visual pathway, Associative Visual Agnosia, Tractography.

1-C-73 *Deciphering the novel role of amyloid-β42 in the nucleus*

Suleyman Akerman[1], Gerhard Multhaup[1]

[1]McGill University

Alzheimer disease (AD) is a debilitating proteinopathy lacking effective early diagnosis, prevention, and treatment. Clinicians must currently rely on the presentation of late-stage events such as cognitive decline, whereas the underlying pathophysiological events likely begin decades before clinical symptoms. The amyloid-β (Aβ) peptides are critical to AD pathogenesis, and intraneuronal accumulation of Aβ is seemingly the earliest detectable event. There is growing evidence that Aβ peptides may have links to defects in the nucleocytoplasmic transport machinery. In fact, the Ras-related nuclear protein Ran, a key molecule that dictates the directionality of this transport, was found to be decreased in the brain of AD patients. Our laboratory has previously described a novel role for Aβ42 in nuclear signaling and gene regulation. We have investigated whether Aβ can modulate Ran protein levels using the same neuroblastoma cell culture model. We have found that Aβ42 specifically caused a reduction in Ran levels. Furthermore, nuclear envelope irregularities were reported in AD brain as well as in Huntington disease. Thus, we hypothesize that Aβ42 could be causing these effects in AD through interference with nucleocytoskeleton protein functions, either in conjunction with tau or by itself.

1-C-74 *Diffusion imaging fibre tractographic analysis for auditory saccadic attention deficit (ASAD) in progression stages of Alzheimer's disease*

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Zipho Godlo[1], Ganesh Elumalai[2], Panchanan Maiti[3], Christina Vadiyala[2], Venkata Harikrishna Yadav Kurra[2], Agunwa Chinonso Godwin[2], Tajnin Mohammad Hashim[2], Ashleigh haughton[2]

[1]Texila American University, [2]Team NeurON - Texila American University, [3]Saginaw Valley State University, MI, USA

INTRODUCTION: The ability of human beings to perceive auditory stimulus in everyday acoustic environments depends on the localization and the identification of relevant sounds. Localization (or) the spatial orientation of the stimulus and relative motor output with saccadic eye and neck movements is analyzed by the tract from Auditory cortex (BA-41, 42) to Premotor Eye-Ear Field [PEEF] (BA-8b), called Auditory-saccadic pathway. Our study aimed on comparative analysis of this pathway in control adults with Alzheimer's Patients, using "Diffusion Imaging fibre Tractography". We used 60 Diffusion Tensor Imaging (DTI) datasets (30 Males and 30 Females), between the age ranges from 55-100 yrs. RESULTS: Study reveals that, bihemispheric detoriation of auditory saccadic pathway fibers were observed in females with AD, as compared to males. Whereas the auditory saccadic fibers are markedly increases in disease progression stages of males AD. CONCLUSION: Present study proves the existence of neurostructural connectivity of Auditory-saccadic pathway (dorsal stream-auditory pathway) and the detoriation of this track leads to cause of Auditory saccadic attention deficit (ASAD) in Alzheimer's Patients. But, the results must to strongly evidence with functional and efficient connectivity analysis in future. Keywords: Auditory-saccadic pathway, Auditory Attention Deficit, dorsal stream-auditory pathway, Premotor Eye-Ear Field, Auditory cortex.

1-C-75 *Cell-cell communication modelling and single-cell RNA sequencing reveal novel interactions within injured nerves that regulate peripheral axon growth*

Jeremy Toma[1], Matt Carr[1], Scott Yuzwa[2], Adelaida Kolaj[1], David Kaplan[1], Freda Miller[1]

[1]The Hospital for Sick Children, [2]University of Toronto

Peripheral nerves promote regeneration of both PNS and CNS neurons, an activity that has been ascribed to nerve-resident Schwann cells. Here, we have used cell surface mass spectrometry and transcriptional profiling, including single-cell RNA sequencing, to identify and computationally model potential paracrine interactions between neurons and cells in control and injured nerves. These analyses show that peripheral nerves make many ligands predicted to act on PNS and CNS neurons, including known and previously uncharacterized ligands. Novel factors predicted to be expressed by Schwann cells - BMP7 and VEGFC - were found to regulate the growth of sensory axons in vitro. Surprisingly, many of these ligands are made by nerve-resident mesenchymal cells, including the endoneurial cells mostly closely associated with peripheral axons. At least some of these mesenchymal ligands, including CCL11 and ANGPT1, promote growth when locally applied on sympathetic axons. These data therefore identify an unexpected paracrine role for nerve

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mesenchymal cells and suggest that multiple cell types in peripheral nerves contribute to creating an environment conducive to neuronal regeneration.

1-C-76 *The Alzheimer risk factor CD2AP regulates APOER2 homeostasis and signaling in brain vasculature*

Milene Vandal[1], Colin Gunn[1], Philippe Bourassa[2], Steven Seungjae Shin[1], Camille Belzil[1], Yulan Jiang[1], Cyntia Tremblay[3], David Bennett[4], Grant Gordon[1], Frédéric Calon[2], Minh Dang Nguyen[1]

[1]University of Calgary, [2]Université Laval, [3]CHU de Québec - Université Laval, [4]Rush Alzheimer's disease Center

Cerebrovascular defects play a key role in Alzheimer Disease (AD). However, the molecular mechanisms underlying vascular impairments in AD remain poorly understood. Polymorphisms in CD2AP are associated with an increased risk for AD. CD2AP encodes for a scaffolding protein that is highly enriched in brain endothelial cells (BECs) and is implicated in receptor trafficking. Based on current evidences, we propose that CD2AP regulates the homeostasis of receptors enriched in the brain endothelium. Specifically, we hypothesize that ApoE receptor 2 (ApoER2) is a CD2AP target and that disruption of the CD2AP-ApoER2 axis in BECs contributes to cerebrovascular dysfunction in AD. Our objectives were 1) to evaluate the levels of CD2AP and ApoER2 in isolated brain microvessels of AD patients, and 2) to study the role of the CD2AP-ApoER2 axis in cerebrovascular functions. We found a reduction of CD2AP and ApoER2 levels in brain microvessels of AD volunteers, and that both decreases correlate with cognitive dysfunction. Using mouse brain and BECs in culture, we discovered that CD2AP functionally interacts with ApoER2 and regulates its levels, processing and signaling. Importantly, activation of ApoER2 promotes vasodilation of penetrating arterioles in brain cortical slices without activating astrocytes and neurons, as demonstrated by two-photon microscopy and calcium imaging. We identified a role for the ApoER2-CD2AP axis in BECs for control of the vascular tone. Dysregulation of this axis may contribute to cerebrovascular defects in AD.

1-C-77 *Subclinical inflammation has distinct behavioral profile*

Theodore Cloutirer[1], Kenzo Yamamoto[1], Marjan Gharagozloo[1], Shaimaa Mahmoud[1], Camille Simard[1], Denis Gris[1]

[1]University of Sherbrooke

Early treatments of diseases correlate with better outcomes and improved quality of life. Neuroinflammation is a common denominator of, practically, all diseases of central nervous system (CNS). Nod-like receptors are among the main regulatory proteins of inflammation. One

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of these proteins, Nlrx1, attenuates inflammation. Using Nlrx1 KO mice, we have developed mice with increased inflammation in the CNS. The objective of this study is to detect significant behavioral changes that reveal pre-symptomatic mice that have increased inflammation. C57/Bl6,2D2, and RAG KO mice were bread with Nlrx1 KO mice and video recorded 24hr/day. The resulting videos were analyzed using the HomeCageScan software. Cluster and factor analysis were used to screen 40 behavioral parameters. Individual behavioral activities were analyzed by two-way ANOVA followed by Tukey test. Behavioral profile of asymptomatic mice with increased CNS inflammation is drastically different from WT healthy mice. As an example, Nlrx1 KO mice sleep twice as much during the day compare to WT and have similar sleep patterns as mice that experience clinical neuroinflammation. Also, they show a 30% increase in awakening and follow the same awakening pattern as mice that have advanced disease confirmed by clinical symptoms. Nlrx1 mice twitch ten times less compared to WT. An automated method of evaluating animal behavior allows for unbiased detection and quantification of the increased inflammatory load in the CNS of otherwise asymptomatic mice.

1-C-78 *Growth differentiation factor 11 promotes survival of retinal ganglion cells in vitro and in vivo*

Hyung-Suk Yoo[1], Usha Shanmugalingam[1], Margarita Lui[1], Patrice Smith[1]

[1]Carleton University

The visual system is a well-established model system to study axon regeneration and cell survival in vitro and in vivo. The use of this model has resulted in the identification of a variety of factors that improve cell survival and axonal growth after axon injury. Growth differentiation factor 11 (GDF11), a transforming growth factor-β (TGF-β) family member, was previously identified as a rejuvenation factor that promoted neurogenesis in aging mice. Previous work has revealed that gdf11 mRNA is expressed in the developing retina, and that GDF11 protein can signal Xenopus retinal ganglion cell (RGC) growth in vitro. Previous work has revealed a striking decline in intrinsic RGC growth potential with age. The mechanisms mediating this dramatic loss of axonal growth ability has fueled significant interest in defining the factors that could contribute to this limitation in growth ability. The potential regenerative effect of GDF11 on mammalian RGCs remain unclear. Experiments were designed to determine whether GDF11 treatment promotes RGC survival and axonal growth using in vitro and in vivo models. Our data revealed that GDF11 administration was sufficient in protecting RGCs both in vitro and in vivo, but did not promote axonal growth. Our data also suggest that GDF11 promotes its neuroprotective effects via activation of phospho-Smad2/3 in vitro.

1-C-79 *ATF4 regulates neuronal death in cellular models of Parkinson's disease*

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Matthew Demmings[1], Sean Cregan[2]

[1]University of Western Ontario/ Robarts Research Institution, [2]University of Western Ontario

Parkinson's Disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra. However, mechanisms underlying this neuronal loss remain largely unknown. ATF4, a key mediator of the Integrated Stress Response (ISR), is a transcription factor that during prolonged activation can induce the expression of several downstream pro-apoptotic target genes. Both oxidative stress and mitochondrial dysfunction are associated with PD and these factors are known to activate the ISR. In this study, we have determined, that both PD neurotoxins (MPP+ and 6-OHDA) and pre-formed alpha-synuclein fibrils (PFFs) elicit the ISR and cause sustained upregulation of ATF4 protein in mouse primary cortical and mesencephalic neurons. Furthermore, we have identified that this increase in protein leads to ATF4-dependent transcriptional activation of known pro-apoptotic genes. Importantly, using neurons derived from ATF4 +/+ and ATF4 -/- mice, we have shown ATF4 to be necessary for neuronal apoptosis and that ATF4-deficient dopaminergic neurons display attenuated cell loss following exposure to PD neurotoxins or PFFs. These novel molecular findings highlight ATF4 and the ISR as a potential therapeutic target in PD.

1-C-80 *Benefits of dancing with Parkinson's for care partners*

Eden Champagne[1], Sarah Ciantar[1], Joseph DeSouza[1]

[1]York University

Parkinson's disease (PD) is a neurodegenerative disorder with no cure, and results in cardinal motor symptoms and non motor symptoms including sleep disturbances, depression, and difficulties with executive functions such as empathy and memory (Hoehn & Yahr, 1967; Dujardin et al., 2004). Investigations of adapted dance interventions for people with PD are growing and show promising results for improving physical abilities and quality of life, as dance strategically employs rhythm, imagery, physical activity, and fosters collective joy (Ehrenreich, 2006; Dhami et al., Westheimer et al., 2015). However, what is still unclear is the effect of these dance classes on the spouses of people with PD, who participate with their partner in the weekly classes. Spouses whose partners suffer with PD often have to take on a caregiver role and face many challenges which can lead to a poorer quality of life, as compared to non-caregivers (Pinquart & Sorensen, 2007). The present research aims to quantify how weekly dance-training benefits the lived experience and quality of life for spouses in the caregiving role. From 2014 to present, 6 dyads (one person with PD, the other their spouse/caregiver) have been tracked empirically pre- and post-dance class (EEG, PANAS-X, UPDRS) across 2-10 testing sessions. It is expected that post-dance class, and over time that for both members of the dyad, positive affect will increase, and distress will decrease. Qualitative interviews will be conducted to gain rich data of lived experience of how dance has influenced relationship health over time.

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1-C-81 *Store-operated calcium entry deregulation in iPSC-derived neural progenitor cells from bipolar disorder patients*

Tristen Hewitt[1], Ryan Hallam[1], Manali Tilak[1], Jennifer Wang[2], Begüm Alural[1], Nina Jones[1], Scott Ryan[1], Steven Sheridan[1], Roy Perlis[3], Jasmin Lalonde[1]

[1]University of Guelph, [2]Massachusetts General Hospital, [3]Harvard University

Calcium is a crucial signaling molecule that accumulates in compartmental sinks like the endoplasmic reticulum (ER). When depleted, the ER refills itself with the help of store-operated calcium entry (SOCE)--a process that results in calcium influx through ORAI channels. Although recognized as a mechanism controlling various pathways in non-excitable cells, the role of SOCE in neural progenitor cells (NPCs) and differentiated neurons has been largely ignored due to the fact that these cell types express many other specialized calcium channels. Recent progress shows, however, that SOCE is not only active in NPCs and neurons but that defect in the function of this signal could play a role in certain brain disorders. Using a collection of iPSC-NPCs derived from bipolar disorder (BD) patients and healthy control individuals, we present evidence for a connection between SOCE, neuronal differentiation, and BD. First, using calcium imaging we uncovered lower level of SOCE activity in NPCs derived from BD patients compared to control lines. This observation prompted us to next examine proliferation and migration of NPCs from each condition with different strategies. Although both processes appeared similar between our different cell lines, we discovered an increase in neurite extension in the BD NPCs while completing a neurosphere assay--a result that we subsequently found to be consistent with data derived from RNA-sequencing (RNA-Seq) and cerebral organoid models. Together, our findings reveal a new pathway that could be contributing to the pathogenesis and pathophysiology of BD.

1-C-82 *Identification of brain cell type proportion changes in whole tissue expression profiles*

Ogan Mancarci[1], Lilah Toker[1], Shreejoy Tripathy[2], Paul Pavlidis[1]

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

Differential expression in whole tissue expression profiles are often used to study neurological disorders. In such studies differential expression can be a result of a uniform changes in gene expression of all cell types, gene expression changes in specific cell types, or changes in cell type proportion. Using our previously published methods for detecting cell type proportion changes from whole tissue expression profiles, we analyze ~400 mouse and human brain whole tissue datasets from the literature to identify conditions that might be causing changes in cell type proportions. Our method summarizes gene expression of cell type markers to get an estimate of

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cell type proportion changes. We also expand this method to include robust quality metrics to reliably separate gene regulation from changes in cell type proportions and identify false positive findings. We identify known cell type proportion changes in neurodegeneretive disorders along with novel changes under a wide variety of conditions ranging from neurological disorders in humans to mouse models.

1-C-83 *Choice of anesthesia substantially influences the intraoperative responses to spinal-cord neuroprostheses*

Amirali Toossi[1], Dirk Everaert[2], Richard Uwiera[2], David Hu[2], Kevin Robinson[3], Ferrante Gragasin[2], Vivian Mushahwar[2]

[1]University of Toronto, University Health Network, [2]University of Alberta, [3]Belmont University

The overall goal of this project was to advance the novel intraspinal microstimulation (ISMS) neuroprosthetic approach towards clinical translation. ISMS aims to restore standing and walking in people with severe spinal cord injuries (SCIs) by activating the spared motor networks in the ventral horns of the lumbosacral enlargement in the spinal cord through an implanted microelectrode array. In animals, ISMS was able to restore weight-bearing, fatigue-resistant standing and walking even after severe SCIs. The first step in the clinical translation of ISMS is to investigate its functional performance in humans in an intraoperative setting. In this study, we tackled a critical requirement for this step and investigated the effect of common pre-clinical and clinical anesthetics on the evoked responses. Experiments were conducted in 7 domestic pigs with ISMS implants. In each animal, the responses to ISMS (stimulation threshold, joint range of motion, and torque) were measured under 3 anesthetic protocols: 1) Isoflurane 2) Propofol 3) Pentobarbital. Washout periods were applied in between to minimize confounding effects. Responses to ISMS were significantly suppressed under isoflurane compared to Propofol and Pentobarbital. Propofol and Pentobarbital allowed the production of large ranges of motion and joint torques which were not statistically different from each other. Therefore, propofol anesthesia is suitable for clinical intraoperative testing of ISMS, and the acquired responses under this protocol will be comparable with preclinical literature using pentobarbital.

1-C-84 *Longitudinal measures of lesion volume correlates with neurobehavioral deficits in a non-human primate model of stroke*

Kathleen Harrison[1], Gabriel Ramirez-Garcia[1], Juan Fernandez-Ruiz[1], Joe Nashed[2], Douglas-James Cook[3]

[1]Universidad Nacional Autónoma de México, [2]Queen's University, [3]Queen's University / Kingston Health Sciences

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Background: Stroke is a leading cause of death and disability. Data from rodent stroke models suggest size and location of ischemic lesions relate to outcomes, but such a relationship is not well established in humans; likely due to the increased importance of white matter in primate brains. This incongruency complicates clinical evaluation of novel therapeutics, as strokes of differing size can produce similar deficits. Only one study has characterised neurological outcome and injury volume in non-human primates (NHPs), but is unfortunately severely under-powered. Methods: Male Cynomolgus Macaques underwent T2 scans prior to, 48 hours, and 30-days post-MCAO. Neurological function was assessed by Nonhuman Primate Stroke Scale (NHPSS). T2 whole lesion volume was calculated per subject. Results: Longitudinal lesion volumes showed positive correlations with NHPSS scores (r = 0.72), whereas remaining brain volumes negatively correlated (r = - 0.70). Following ROI parcellation, NHPSS outcome correlated to lesion volume at 30- days with multiple brain regions. Importantly, strongest relationships were found with damage to temporal white matter (r = 0.80). Conclusions: This supports literature that stroke regionality and severity predicts outcome. The NHP model provides a fairly homogenous stroke, with outcomes correlating with severity. This research represents an important step in translational research in evaluation of the NHP stroke model. We propose that similar methods are implemented in human clinical trials.

1-C-85 *Alzheimer's disease biomarkers in cerebrospinal fluid of nonhuman primates*

Emma Robertson[1], Susan Boehnke[1], Brittney Armitage-Brown[1], Robert Wither[1], Natalia Lyra e Silva[1], DJ Cook[1], Ron Levy[1], Fernanda De Felice[1], Douglas Munoz[1]

[1]Queen's University

Alzheimer's disease (AD) pathology, such as amyloid plaques and neurofibrillary tangles, are present in humans before the onset of behavioural symptoms (Sperling et al., 2011). Markers for these pathological changes can be analyzed in cerebrospinal fluid (CSF). Changes in CSF levels of amyloid-ß 1-40 (Aß40), amyloid-ß 1-42 (Aß42), total tau proteins (tTau), phosphorylated tau (pTau), and neurofilament light (NFL) have been implicated as biomarkers of human AD. Here, we sought to determine levels of these biomarkers in a colony of naïve, control cynomolgus and rhesus macaque monkeys (n=30) to establish baseline values to compare to disease models. CSF samples were collected through lumbar punctures or a lumbar port. Baseline values of Aß40, Aß42, tTau, and pTau showed some inter-subject variability, but were similar between species and to published human values. Importantly, we found that repeating lumbar punctures at different time points elevated NFL (~300%) but did not elevate other biomarkers. Once baseline levels of Aß40, Aß42, tTau, pTau and NFL were established, we also tracked CSF biomarkers in a recently developed monkey model of AD (Forny-Germano et al., 2014, Batista et al., 2018). In monkeys receiving injections of AßOs, CSF AD biomarkers were elevated, but not in monkeys receiving vehicle injections. Thus, these changes in CSF may be reflective of developing AD-related

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pathology in the brain and will allow us to investigate disease progression, pathological mechanisms and test novel therapeutics.

1-C-86 *Quantifying upper limb bradykinesia, rigidity and postural instability using the KINARM Robot in Parkinson's Disease*

Pauline Gaprielian[1], Ron Levy[1], Stephen Scott[1], Catherine Lowry[1], Giovanna Pari[1], Stuart Reid[1]

[1]Queen's University

The use of integrated robotic technology to quantify the spectrum of motor symptoms of Parkinson's Disease (PD) has the potential to facilitate objective assessment that is independent of clinical ratings. The Kinesiological Instrument for Normal and Altered Reaching Movement (KINARM) exoskeleton robot was used to quantify upper limb PD motor symptoms of bradykinesia, rigidity and postural instability in order to differentiate patients from healthy controls. We used a test battery of four KINARM specific robotic tasks and task parameters to compare patient and control performances. Twenty-six patients were evaluated OFF dopamine replacement therapies (DRTs) (after a minimum 12-hour washout period from their last dose). Their robotic task performance was compared against age matched controls. The results of the receiver operating characteristic curve showed a 94% discriminatory ability for bradykinesia, 90% discriminatory ability for rigidity and 68% discriminatory ability for postural instability for differentiating patients from controls. Upon comparison of z-scores, it was found that PD patients deviate two standard deviations or more away from average normal performance. Finally, KINARM specific robot task performance was correlated with clinical ratings. In summary, this study demonstrates that KINARM's ability to quantify PD motor signs and differentiate patients from healthy controls. Future studies will be focused on determining if this platform can quantify the effects of DRTs and deep brain stimulation.

1-C-87 *Investigating adult neurogenesis in the Parkin/PolG mouse model of Parkinson's Disease*

Maria Bilen[1], Richard Harris[1], Mohamed Ariff Iqbal[1], Ruth Slack[1]

[1]University of Ottawa

Adult neurogenesis is a continuous process of formation and integration of neurons in the adult brain. Neural stem cell (NSC) proliferation and differentiation in the subgranular zone (SGZ) contributes to cognitive function. Defects in neurogenesis are hallmarks of aging and neurodegenerative disease. Recent discoveries highlight the role of mitochondrial dynamics in the regulation of gene expression and neurogenesis. Parkinson's disease (PD) is a

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neurodegenerative disorder characterized by the loss of dopaminergic neurons of the substantia nigra leading to motor impairment. Cognitive decline and anxiety are non-motor symptoms manifesting in early stages of the disease, indicating that adult neurogenesis is compromised. A common mutation linked to PD is observed in the Parkin gene, a regulator of mitophagy. Using a Parkin-null mouse model we report effects of mitochondrial dysfunction on neurogenesis. However, the mouse model fails to show dopaminergic neuron degeneration. Therefore, we designed a breeding strategy combining Parkin with a mutated PolgA gene, a mtDNA polymerase subunit responsible for proofreading and model shown to develop dopaminergic degeneration. Analyses in vivo were performed on the SGZ to examine defects in NSC self-renewal and proliferation, while NSCs were grown in vitro to investigate an alteration in metabolism. Further studies need to be performed to identify the signaling molecules linking mitochondrial function to neurogenesis. These molecules can then constitute therapeutic targets in PD. This study was supported by a CIHR Grant to RSS.

1-C-88 *Accumulation of modifications in the tau core region during the tau aggregation process in Alzheimer's disease*

Pieter Beerepoot[1], Hendrik Wesseling[1], Waltraud Mair[1], Michaela Svrdlikova[1], Long Cheng[1], Hanno Steen[1], Judith Steen[1]

[1]Boston Children's Hospital/Harvard Medical School

Although the presence of tau aggregates is a pathological hallmark of Alzheimer's disease (AD), the aggregation process is not well understood. Pathological tau undergoes extensive post-translational modification (PTM), creating numerous tau proteoforms with distinct structural and functional properties. We characterized the tau PTM landscape using quantitative and qualitative mass spectrometry in AD (n=30) and control (n=30) human brain tissue preparations. Sarkosyl fractionation, size-exclusion chromatography, and immuno-purification were used as complimentary methods to yield preparations ranging from soluble monomeric tau to insoluble fibrillar tau to assess the sequence of modification. We also characterized the seeding activity of the different tau preparations in HEK293 biosensor assays. Lastly, we used immunoprecipitation to immunodeplete specific proteoforms of tau and tested seeding activities of the depleted lysates and eluates. Analysis of size-resolved tau showed an accumulation of PTMs associated with the formation of tau aggregates. Strikingly, we observed acetylation and ubiquitination in the core region of tau in different preparations of seeding competent tau, but not in seeding incompetent tau from control or AD brain tissue. Immunoprecipitation of ubiquitinated proteins resulted in a seeding competent preparation that was highly abundant in tau. Based on these results and the known cryo electron-microscopy structure of tau filaments, we propose a model where accumulation of charge neutralizing PTMs promotes the formation of tau aggregates.

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1-C-89 *Systematic phenomics analysis of ASD-associated genes defines shared and unique functions and identifies parallel genetic networks underlying hypersensitivity and impaired habituation*

Troy McDiarmid[1], Manuel Belmadani[1], Joseph Liang[1], Fabian Meili[1], James Rand[2], Kota Mizumoto[1], Kurt Haas[1], Paul Pavlidis[1], Catharine Rankin[1]

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

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

1-C-90 *Retrograde amnesia and reduced perseveration in the Morris water task after repeated seizures*

Kassidy Roberts[1], Lianne Brandt[1], Hugo Lehmann[1], Neil Fournier[1]

[1]Trent University

Research on the relationship between memory and epilepsy has found that seizure activity produces retrograde amnesia (RA). These studies, however, have typically focused on memories being disrupted during the period of cellular consolidation (CC). Few studies have addressed whether repeated seizures impair memories that have completed the consolidation process and it is unclear whether these deficits in memory are transient or long-lasting. To address this, Long

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Evans rats were trained in the hidden platform version of the Morris Water Task. Two days after training, beyond the CC window, the rats were treated with the chemo-convulsant pentylenetetrazole (PTZ) every other day for 2 weeks. The rats were then assessed for retention 2 or 14 days after the treatment, with the longer retention interval assessing persistence of the impairment. Next, the rats were retrained on the same location followed by a new location (reversal). We found that spatial memories outside the window of CC are subject to seizure-induced RA and that this deficit persists up to 14 days after seizure termination. The seizures, however, did not impair new learning, with the exception that the rats that suffered the seizures showed faster search cessation of the original platform location during the reversal session. Hence, our findings suggest that memories currently believed to be more resistant to brain injury, those outside of CC, remain sensitive to repeated seizures. Moreover, the seizures reduced perseveration or persistence in using acquired information, a possible executive function deficit.

1-C-91 *Effects of dance therapy on balance and affect in Parkinson's disease*

Sarah Ciantar[1], Eden Champagne[1], Benjamin Patrick[1], Karolina Bearss[1], Rebecca Barnstaple[1], Tenzin Chosang[1], Josilyn Weidman[1], Olivia Morson[1], Joseph DeSouza[1]

[1]York University

Introduction: Dance as a therapy and intervention to support traditional pharmacological practices for people with Parkinson's Disease (PD) has grown support with previous research. Ours examines behavioural and functional brain changes in individuals with PD through learning novel choreography as measured by motor, balance, and affect scales. Methods: People diagnosed with PD (N=22; MDxYears=8.11, SD= 5.42) between the ages of 52-76 (M=67.91, SD=5.43) participated in weekly Dance for PD® classes for 10 months. The Berg Balance Scale (BBS), Timed Up and Go (TUG), and Geriatric Depression Scale (GDS) were administered 3 times at two-month intervals, to assess balance and gait. Resting-state electroencephalography (rsEEG) was obtained before and after 75-minute dance classes. Results: BBS and TUG motor tasks showed improvements on balance scores both in pre- and post-class comparisons as well as over the 3 time points ($p<0.05$). In non-motor symptoms, we observed a decreasing trend in GDS scores ($p<0.01$;$p<0.05$; $p=0.054$). With rsEEG we found a significant increase in global alpha peak frequency measures in pre- and post-class comparisons ($p<0.05$). Discussion: This study provides novel insights into the benefits of dance in people with PD, through correlating recorded improvements in the GDS questionnaire to observed changes in motor and balance measurements in TUG and BBS assessments. Symptom improvement may be the result of the holistic nature of the dance class, which integrates social, physical, and cognitive elements.

1-C-92 *Continuous spike waves of slow-wave sleep extends into adulthood*

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Soumia Djarir[1], Inna Voloh[1], Dragna Jovanovic[1], Mohaddeseh Gholizadeh[1], Paul Hwang[2]

[1]University of Toronto, [2]University of Toronto, North York General Hospital

Objective: Overnight PSG with video-EEG in a 19 year old LH woman showed almost continuous spike-wave discharges 50-60% of sleep, mainly in slow-wave sleep (N2 & N3), not in REM or wakefulness. Methods: Polysomnography with video-EEG in 10-20 + zygomatics overnight in sleep lab, each channel digitized 500/ch/sec, 1-70 Hz. Results: She has a history of afebrile seizures at 3.5 years, seizures controlled on AEDS (PB, PHT then VPA) currently on valproate only 30mg/kg/day with good seizure control, but is cognitively challenged in school, 1-2 years behind in language and math, intending to graduate at age 21 years from high school at a basic level. Conclusion: Although not as severe as the pattern of ESES, the EEG pattern of CSWSWS is associated with cognitive impairment and learning disorder. Its pathophysiology requires further elucidation.

1-C-93 *Evaluation of the comparative effect of epigallocatechin gallate alone and in combination with progesterone in experimental model of cerebral ischemia in mice*

Harjeet Kaur[1], Amitava Chakrabarti[2]

[1]Panjab University, [2]PGIMER, Chandigarh

Stroke is one of the major challenges to health and the reason for increasing disability-adjusted life years (DALYs). Interruption of blood supply to brain results in neurological damage and behavioral impairment. The neuroprotective effect of Epigallocatechin gallate (EGCG) alone and in combination with progesterone were examined in bilateral common carotid artery occlusion model of stroke in Swiss albino mice. As compared surgically treated group, EGCG alone and combination group of EGCG and progesterone showed significant neuroprotection by ameliorated oxidative stress, proinflammatory cytokines and improved histopathological score in the acute phase of the study. Four days, EGCG and combination group post-stroke treatment significantly attenuated behavioral alterations. EGCG and combination treatment of progesterone also significantly reduced brain infarction and brain edema in BCCAO model in Swiss albino mice. These results showed that the EGCG alone and in combination with progesterone reduced neuronal death after cerebral ischemia in mouse brain.

1-C-94 *Genetic alterations in brain tissue samples from living Parkinson's disease patients*

Simon Benoit[1], Hu Xu[1], Roumiana Alexandrova[2], Bhooma Thiruvahindrapuram[2], Gaganjot Kaur[2], Matthew Hebb[1]

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[1]University of Western Ontario, [2]The Hospital for Sick Children

Whole-transcriptome sequencing has become feasible at a fraction of the time and cost offering a new avenue for biomarker discovery for neurodegenerative diseases. The central nervous system of living PD patients is the ideal source of tissue for such studies, but access is limited. Small volume brain biopsies obtained during deep-brain stimulation surgery for PD offer a novel and feasible source of such tissue. Total RNA was extracted from cortical biopsies in 6 patients with PD and 5 controls, then sequenced on Illumina HiSeq 2500. We analyzed for differentially expressed genes (DEGs) and pathway alterations using edgeR (v.3.8.6) and validated using quantitative PCR. SpliceSeq (v2.1) was used to detect differential alternative splicing (AS) events and variant calling was performed using GATK (v1.128) and VarAFT (v.2.14). Overall, analysis raised 376 DEGs, 646 AS events and several rare or unique variants in PD gene loci. Genes highlighted by these analyses include mediators of immune and inflammatory response such as IL10, IL1R2, and NFKBIA; reactive oxygen scavenging metallothioneins 1F and 1G; growth factors including GDNF, PEDF and FGF18; and the apoptosis inducing ligand TRAIL and its receptor TRAILR1. To our knowledge this is the first demonstration of differential CNS gene expression and AS in cortical samples from living PD patients. Pooled together, DEGs, variants and AS events identified by this study have the potential to uncover a unique gene signature specific to PD, key to giving rise to precise diagnostic and prognostic clinical assays.

1-C-95 *Bi-rhythmic biomimetic electrical stimulation paradigm for seizure suppression*

Uilki Tufa[1], Liang Zhang[2], Peter Carlen[3], Berj Bardakjian[1]

[1]University of Toronto, [2]University Health Network, [3]Krembil Research Institute

Epilepsy affects about 300,000 Canadians. About 25% of patients are intractable to anticonvulsant drugs, do not meet surgical criteria and have no adequate treatment. Electrical stimulation can be an effective alternative treatment. Clinical trials have demonstrated the safety of thalamic stimulation using a high frequency stimulus with limited efficacy. Our group has previously shown, in silico, the success of stimulation with a biomimetic therapeutic signal, outperforming mono-rhythmic waveforms. In this study we aim to extend our findings in vivo and investigate a thalamic continuous stimulation paradigm using a biomimetic signal, where the amplitude of a high frequency rhythm is modulated by the phase of a low frequency rhythm forming a cross-frequency coupled (CFC) waveform, to suppress seizure-like events (SLEs) in a kindled mouse model. Bipolar electrodes were implanted in the CA3 and in the ipsilateral medial dorsal nucleus, allowing for stimulation and EEG recordings. A webcam was used for monitoring animal motor behavior. Mice were kindled daily through unilateral CA3 stimulations, reaching stage 5 SLEs. To test suppression, thalamic stimulation using a CFC waveform was applied continuously for 15 minutes, followed by hippocampal stimulation to evoke an SLE. We found a 1Hz-100Hz phase-amplitude CFC waveform to be effective in suppressing SLEs (confirmed by EEG and video analysis) and

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increasing the after discharge threshold. We aim to fine tune parameters and investigate this effect in more animals as well as a spontaneous recurrent seizure mouse model.

1-C-96 *The anti-aging protein klotho mitigates cytotoxicity of β-amyloid peptides in cellular model of Alzheimer's disease*

Mohsen Sedighi[1], Tourandokht Baluchnejadmojarad[1], Mehrdad Roghani[2]

[1]Iran University of Medical Science (IUMS), [2]Shahed University

Introduction: Alzheimer's disease (AD is a neurodegenerative disease characterized by progressive neuronal loss and inflammation which is affected memory, language, behavior and cognition. Klotho protein is the product of an aging-suppressor gene that its overexpression could protect neurons against oxidative damage and neural inflammation. Material and methods: The present study was performed to investigate the effect of pretreatment with different concentration of klotho (0.5, 1 and 2 μM) on SH-SY5Y neuroblastoma cells as a cellular model of AD induced by Aβ (1-42). For induction of cellular model of AD, Aβ (1-42) was added to SH-SY5Y cell medium. Concentration of IL-1β, IL-6, TNF-α were measured using ELISA Results: Our results showed that Aβ (1-42) increases IL-1β, IL-6, TNF-α concentration in AD cells compared to the control group ($p<0.05$). Also, pretreatment of SH-SY5Y cells with klotho 2 μM diminished neural inflammation in AD cells through the decrease of IL-1β, IL-6, TNF-α compared to the control group ($p<0.05$). Conclusion: Taken together, our results suggest that klotho prevents cell damage induced by Aβ (1-42) in SH-SY5Y cells. It seems that the beneficial effects of klotho are mediated through the alleviation of inflammatory cytokines release.

1-C-97 *Activity dependent neuroprotection in the acute phase after stroke*

Matilde Balbi[1], Dongsheng Xiao[1], Louis-Philippe Bernier[1], Matthieu Vanni[1], Jamie Boyd[1], Jeffrey LeDue[1], Brian MacVicar[1], Timothy Murphy[1]

[1]University of British Columbia

Stroke represents a leading cause of death and disability worldwide. Optogenetic stimulation used to enhance stroke recovery has shown potential benefits when applied weeks after injury. However, benefits of acute brain stimulation have not been reported. Changes in gamma oscillations (20-50 Hz) have been observed in several neurological disorders but the relationship between gamma oscillations and cellular pathologies is unclear. We investigated the effect of the gamma-wave modulation in the acute phase - within 1 hr - after stroke. We combined multimodal approaches employing optogenetics in conjunction with laser speckle imaging, two photon microscopy, electrophysiology and behavioral tasks. Transgenic VGAT-ChR2 mice were

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implanted with a transcranial chronic window and subjected to photothrombotic stroke while awake in the target area of somatomotor cortex. Optogenetic stimulation at 40 Hz ipsilateral to the stroke side resulted in a significantly higher increase in blood flow over the course of the first week following stroke (Stroke n= 8 vs Stroke + stimulation n= 10: p= 0.0148). Stroke area and stroke volume were significantly reduced in mice that received the stimulation (Area: Stroke n= 8 vs Stroke + stimulation n= 10, p= 0.0010; Volume: Stroke n= 8 vs Stroke + stimulation n= 10, p= 0.0249). Assessment of motor function showed a significant improvement over time in mice that received stimulation (NDS: Stroke n= 8 vs Stroke + stimulation n= 10, p< 0.0001. Tapered beam test: Stroke n= 9 vs Stroke + stimulation n= 10, Group x time effect: p <0.0001). Microglia activati

1-C-98 *Unstable stalled polysomes underlie dysregulated protein synthesis in human IPSC-derived Fragile X neurons*

Jesse Langille[1], Gilles Maussion[1], Thomas Durcan[1], Wayne Sossin[1]

[1]McGill University

Neurons have the capacity to store information through modification of their connection strengths, a process termed synaptic plasticity. Lasting forms of synaptic plasticity involve local changes in the synaptic proteome. Polysome complexes paused following translation initiation and thus containing partially translated mRNAs are termed stalled polysomes and have been implicated in local protein synthesis. While stalled polysomes have been well described in rodents their existence and characterization in human neurons is largely unknown. We did experiments comparable to those done in rodents in human IPSC-derived neurons. We show human IPSC-derived neurons have stalled polysomes which co-localize with Fragile X mental retardation protein (FMRP). FMRP is associated with translational repression, perhaps through polysome stall stabilization, and is absent in Fragile X syndrome a common form of autism spectrum disorder and intellectual disability. Translation is elevated in Fragile X syndrome and we suggest this elevation may be caused in part by unstable, 'leaky', stalled polysomes. In line with this suggestion we show neurons from Fragile X patient IPSCs contain fewer stalled polysomes and increased translation. Further, levels of Map-1b, an mRNA shown to be associated with stalled polysomes, was elevated in Fragile X cultures. Thus, atypical stalled polysome function and associated translational dysregulation may contribute to the Fragile X syndrome phenotype.

1-C-99 *Effect of docosahexaenoic acid (DHA) at the enteric level in a synucleinopathy mouse model*

Jérôme Lamontagne-Proulx[1], Katherine Coulombe[2], Cédric Guyaz[3], Mélissa Côté[2], Cyntia Tremblay[2], Frédéric Calon[3], Denis Soulet[2]

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[1]Centre hospitalier de l'université Laval, [2]CHU de Québec - Université Laval, [3]Université Laval

The main neuropathological feature of Parkinson's disease (PD) is the aggregation of α-synuclein protein (α-syn). PD could start with the deposition of α-syn in the enteric nervous system (ENS) resulting in gut dysfunction. It has already been reported that a diet enriched with docosahexaenoic acid (DHA) acts as a neuroprotective agent in the brain in models of PD and may have an impact on the aggregation of α-syn. Thus, we want to study the effect of DHA supplementation on the α-syn protein at the peripheral level. We believe that a diet rich in DHA would reduce the progression of the disease by targeting dopaminergic (DA) neurons in the intestine. To verify our hypothesis, the Thy1-aSyn mouse, which overexpressed human α-syn, was fed with either a control, low or high DHA diets. Guts were collected to assess the effect of the various diets on the intestine of this PD mouse model. Our data show a lower level of DA neurons in the ENS of Thy1-aSyn mice with control diet compared to wild-type animals. This decline in DA neurons is prevented when Thy1-a-syn mice are fed with a DHA-rich diet compared to control diet. Interestingly, a DHA receptor, GPR120, was highly expressed in myenteric neurons, suggesting that this receptor could mediate the neuroprotective effects of DHA. In conclusion, DHA acts as a neuroprotective agent avoiding the loss of DA neurons in the myenteric plexus. The Thy1-a-syn model needs to be characterized further to better understand the mechanisms of action of DHA.

1-C-100 *Neuroprotection and immunomodulation in the gut of parkinsonian mice with a plasmalogen precursor*

Jérôme Lamontagne-Proulx[1], Jordan Nadeau[1], Tara Smith[2], Mélanie Bourque[1], Sara Al Sweidi[1], Dushmanthi Jayasinghe[2], Shawn Ritchie[2], Thérèse Di Paolo[1], Denis Soulet[3]

[1]Centre hospitalier de l'université Laval, [2]Med-Life Discoveries, [3]CHU de Québec - Université Laval

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. It is typically associated with motor symptoms originating from the degeneration of nigrostriatal dopamine (DA) neurons. Early stages of PD have been associated with an alteration in DA production in intestinal DAergic neurons along with inflammation. Interestingly, decreased serum concentrations of ethanolamine plasmalogens (PlsEtn) have been reported in PD patients. Ethanolamine plasmalogens play a role in vesicular fusion and release during neurotransmission, and store neuroprotective polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and are strong anti-oxidants, highlighting areas of potential therapeutic interest. Docosahexaenoic acid is known to play important roles in both the central nervous and peripheral systems, in addition to acting as a precursor of several molecules that regulate the resolution of inflammation. The present study investigated the neuroprotective and anti-inflammatory properties of the DHA-containing PlsEtn precursor, PPI-1011, in the intestine of 1-methyl-4-phenyl-1,2,3,6-

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tetrahydropyridine (MPTP)-treated mice. Treatment with PPI-1011 prevented the MPTP-induced decrease in PlsEtn levels. In addition, it prevented the loss of tyrosine hydroxylase expression and reduced the infiltration of macrophages in the myenteric plexus. These results suggest that PPI-1011 has neuroprotective and anti-inflammatory properties in the gut and indicate its potential utility as a treatment for both early and more advanced stages of PD.

1-C-101 *Evaluating efficacy of small molecules predicted by artificial intelligence to reduce a-synuclein oligomers*

Kevin Siyue Chen[1], William Ryu[1], Suneil Kalia[1], Lorraine Kalia[1]

[1]University of Toronto Faculty of Medicine

Background:Parkinson's disease (PD) is an incurable neurodegenerative movement disorder defined, in part, by intracellular aggregates of the protein α-synuclein (α-syn) within dopaminergic neurons. Using IBM Watson artificial intelligence, we previously generated in silico predictions of approved drugs that may inhibit formation of small aggregates of α-syn, or oligomers, which contribute to neurodegeneration in PD. Here, we utilized two experimental models to assess the efficacy of highly-ranked compounds: a cell-based protein-fragment complementation assay of α-syn oligomerization in vitro, and a Caenorhabditis elegans model of α-syn-mediated neurodegeneration in vivo. Methods: Human neuroglioma H4 cells expressing α-syn tagged with either N- or C-terminal fragments of Gaussia luciferase were treated with drug for 24 hours. Luciferase activity was measured as a surrogate of α-syn oligomer levels. C. elegans expressing either human A30P α-syn or GFP control in dopaminergic neurons were synchronized and drug treated for 72 hours. Motor impairment due to α-syn expression was recorded and quantified. Results: We found that the mTOR inhibitor rapamycin, which was highly-ranked by IBM Watson and previously shown to inhibit α-syn toxicity in experimental models, lowered α-syn oligomer levels in cells and reduced α-syn-mediated motor impairment in C. elegans. Furthermore, we demonstrated efficacy for other highly-ranked drugs in our models. Significance: Our findings suggest that artificial intelligence may be a useful tool for streamlining drug repurposing endeavours for PD.

1-C-102 *Optic Ataxia in Alzheimer's: Structural alterations and their underlying substrates in correlations with "How" stream Visual Pathways*

Ganesh Elumalai[1], Divya Singh[2], Panchanan Maiti[3], Geethanjali Vinodhanand[1], Nitisha Dyal[2], Valencia Lasandra Camoya Brown[2], Nitya Akarsha Surya Venkata Ghanta[1]

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[1]Team NeurON - Texila American University, [2]Texila American University, [3]Saginaw Valley State University, MI, USA

Optic ataxia is a neurological condition, manifestations with disturbances in visual guided hand movements on reaching a target object. It is more prevalent in Alzheimer Patients, and previous studies are failed to provide a substantial evidences for neural structural relations to this symptoms. In this research, Team NeurON, attempted to correlate the dorsal stream visual pathway with Optic Ataxia in Alzheimer's Patients. The study was carried through "Diffusion Imaging Fiber Tractography" and involves 60 DTI datasets from control and Alzheimer Patients (50-70 yrs) with the symptoms of Optic Ataxia. The fibers were traced, and confirmed the structural alterations and their underlying substrates for Optic Ataxia, in correlations with "How" stream Visual Pathways from Visual cortex (BA 17,18 &19) to Superior Parietal Lobule (BA 7). Observations: It was observed that fibers of the females of the control group was higher when compared to the males. However, on completion, it was noted that females displayed more plummet changes in numbers and volumes of "how stream - visuomotor coordination pathway", when compared to the males. Results: In conclusion, based on our observations, destructions in the visuomotor coordination pathway were identified, and believed as an underlying substrates for Optic ataxia in Alzheimer patients. However, for better understanding of this findings, functional and effective connectivity analysis must be recommended. Keywords: Diffusion imaging fiber Tractography, "Dorsal" stream pathway, Superior Parietal Lobule, Striate cortex, "How" stream pathway.

1-C-103 *Neural- derived biomarkers for antidepressant drug response from plasma exosomes.*

Saumeh Saeedi[1], Corina Nagy[1], Jean-Francois Theroux[1], Marina Wakid[1], Naguib Mechawar[2], Gustavo Turecki[1]

[1]Douglas Institute, McGill University, [2]McGill University

Background: The most common treatment for major depressive disorder (MDD) is antidepressant drug therapy (ADT), yet 60% of patients do not respond to first trials with ADT. As a result, biomarker discovery is a prominent aspect of this field; however most of the research is limited to peripheral tissues, leaving questions about its relevance to MDD. Neural-derived exosomes (NDE) from plasma can provide information regarding central changes resulting from ADT response. MicroRNAs (miRNA) are exosomal cargo which may influence recipient cells. Differential miRNA profiles can potentially act as biomarkers, and provide mechanistic insight into changes occurring as a result of ADT response. Methods: This pilot study uses plasma from 10 controls, 5 ADT responders, and 5 non-responders. Exosomes were isolated and divided to produce a total exosome fraction and an immunoprecipitated NDE fraction using marker L1CAM. RNA from exosomes was extracted, and libraries were made following the 4N-small RNA-Seq (Galas)

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protocol and sequenced on the Illumina platform. Results: Results suggest that NDE exosomes are smaller than the total pool of exosomes. Also, exosomes from MDD patients are significantly smaller than controls in both total and NDE fractions. We have identified a miRNAs that are highly enriched in NDE and that overlap with miRNAs present in brain. Differential analysis shows many hits for follow-up. Conclusions: Isolating NDE from plasma provides a valuable resource for biomarker discovery. Our ongoing work aims to provide a neural miRNA profile in MDD, and profiles of ADT.

1-C-104 *Logopenic aphasia tau pathology: An observation on phonological loop fiber-specific white matter reductions in Alzheimer's disease - Is it a causal or casual link?*

Venkata Harikrishna Yadav Kurra[1], Ganesh Elumalai[1], Panchanan Maiti[2], Zipho Lonwabo Godlo[1], Christina Vadiyala[1], Agunva Chinonso Godwin[1], Geethanjali Vinodhanand[1], Nitya Akarsha Surya Venkata Ghanta[1]

[1]Team NeurON - Texila American University, [2]Saginaw Valley State University, MI, USA

Introduction: Logopenic Aphasia (LA), a variant of primary progressive aphasia characterized with difficulty in retrieving precise words, names, or numbers and sentence repetition. Previous studies detailed that 50% of LA patients had (Alzheimer's disease) AD pathology, and characteristics of LA synchronize with language impairments in AD. Researchers believed that, the atrophy of Phonological loop (A sensorimotor circuit that includes auditory regions, the inferior parietal lobe, and Broca's area, which integrates phonological processing and executes motor output) cause LA. Methodology: We focused on structural connectivity of Phonological loop using "Diffusion Imaging fiber Tractography" with 60 DTI datasets (30 Males and 30 Females) of both control and progressive stages of Alzheimer's, with the age range 55-120 years, and made an attempt to correlate the Logopenic aphasia, with phonological loop fiber-specific white matter reductions in early AD. Conclusion: Overall progressive diminution were observed in the phonological loop of males and left hemispheric deterioration is markedly seen in terms of both fibers and tract volume (significant at $p < 0.05$). Current study, also reveals that contralateral adaptation are more pronounced in AD males than in females AD. Based on our analysis on phonological loop in AD, Logopenic aphasia may present as clinical marker for early Alzheimer's. These findings must be vindicated with functional MRIs analysis. Keywords: Logopenic Aphasia, Diffusion Imaging fiber Tractography, Wernicke's area, Broca's area, phonological loop tract.

1-C-105 *Incentive-dependent waiting impulsivity failure in stimulant addiction*

Peter Zhukovsky[1], Sharon Morein-Zamir[2], Chun Meng[1], Jeffrey Dalley[1], Karen Ersche[1]

[1]Cambridge University, [2]Anglia Ruskin University

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Background: Impaired impulse control is a key underlying feature of stimulant drug addiction. Animal research suggests that impairments in corticostriatal circuits and corresponding waiting impulsivity failures facilitate drug abuse. Hypothesizing differences in task-related brain activation in these groups, we investigated neural substrates of waiting impulsivity (defined as premature responses) in stimulant dependent individuals (DSM-IV diagnosis, n=41) and healthy controls (n=42). Methods: We adopted a novel analysis strategy of a well-validated measure of reward anticipation, monetary incentive delay task, to reveal neural correlates of premature responses using mass univariate GLM and dynamic causal modelling (DCM) in task-based fMRI. Results: While we found no group differences in a monetary context, in the drug context substance dependent individuals made more premature responses and showed greater activation in the insular cortex, the anterior cingulate cortex and portions of the striatum than control participants. DCM showed that healthy controls recruit the same networks in the money context as substance dependent individuals in the drug context. Conclusion: Drug-related stimuli carry greater incentive salience for stimulant addicts and are more potent at eliciting impulsive responses in this group than in healthy controls. However, the networks involved in processing waiting impulsive errors in the respective context are strikingly similar in healthy and drug addicted individuals.

1-C-106 *Adiponectin can rescue hippocampal synaptic plasticity in a mouse model of Fragile X Syndrome*

Luis Eduardo Bettio[1], Elizabeth Brockman[1], Suk-Yu Yau[2], Brian R Christie[1]

[1]University of Victoria, [2]The Hong Kong Polytechnic University

Fragile X Syndrome (FXS) is the most common form of inherited intellectual disability and a leading cause of autism. This neurological condition is caused by the transcriptional silencing of the Fmr1 gene, which codes for fragile X mental retardation protein (FMRP, a negative regulator of protein translation). The lack of FMRP is associated with an overactivation of mTOR signaling in the brain, which in turn leads to the excessive translation of several proteins that regulate spine structure and function. Treatments that increase AMPK activity hold promise for rescuing some of the deficits in synaptic plasticity seen in FXS. AMPK is a highly conserved protein that acts as an energy sensor and regulates several processes impaired in FXS such as mTOR activity, autophagy, insulin signaling and mitochondrial function. In the present study, we investigated the influence of adiponectin (APN, an adipocyte-derived hormone that stimulates AMPK activity) on deficits in synaptic plasticity induced by the lack of FMRP in mice. Short-term incubation with APN (10 min, 50 nM) was able to reverse deficits in both long-term potentiation (LTP) and long-term depression (LTD) induced by the lack of FMRP. Conversely, we found that prolonged incubation with APN (1.5-3 h, 50 nM) exacerbated deficits in LTP. Our findings indicate that APN may be a promising treatment for the management of FXS, but further studies are necessary to elucidate the optimal mode for delivery and timing of treatment.

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1-C-107 *Cellular and behavioural characterization of a novel rat model of concomitant traumatic brain and spinal cord injuries.*

Morgane Regniez[1], Valerie Mongrain[2], Marina Martinez[1]

[1]Centre de Recherche de l'Hôpital du Sacré-Coeur de Montréal, [2]Université de Montréal

Traumatic injuries to the brain (TBI) or spinal cord (SCI) can lead to long-term disability. Although the epidemiology, medical complications, and prognosis of isolated TBI and SCI have been described, there are limited data for patients that suffer from concurrent TBI and SCI. Our hypothesis is that combined TBI and SCI will interact to impact recovery of motor, cognitive, and sleep functions. Our goal is to examine the behavioural and neurobiological effects of concurrent TBI and SCI. By using a novel clinically-relevant rat model of TBI/SCI, we will determine: 1) the extent to which TBI affects the functional outcome of SCI by evaluating sleep, motor, cognitive and emotional functions (e.g., electroencephalography, open field, object recognition, sucrose preference); 2) the neurobiological mechanisms by which TBI affects the recovery process of SCI, by assessing inflammatory processes and plasticity pathways (e.g, immunohistochemistry). We expect that 1) TBI and SCI share common pathophysiology, which will be exacerbated when TBI and SCI are concomitant; 2) Concomitant TBI and SCI will significantly delay the recovery of psychomotor functions, compared to TBI or SCI alone; and 3) Concomitant TBI and SCI will significantly increase the inflammatory responses. This study will allow to validate a new animal model of concomitant TBI and SCI and will provide the first characterization of the physiopathology sustaining the psychomotor deficits induced by TBI and SCI. Our research will facilitate the implementation of specific "dual diagnosis" standardized tools.

1-C-108 *CRISPR-Cas9 gene editing of CDK5RAP2 in human pluripotent stem cells and formation of cerebral organoids for disease modeling*

Leon Chew[1], Adam Añoneuvo[1], Adam Hirst[1], Erin Knock[1], Allen Eaves[1], Terry Thomas[1], Sharon Louis[1], Vivian Lee[1]

[1]STEMCELL Technologies Inc

Modeling human disease using human pluripotent stem cells (hPSCs) and CRISPR-Cas9 gene editing, are emerging as important tools to study pathogenesis.Here we used the ArciTect CRISPR-Cas9 system to generate hPSC clones harbouring a truncation of CDK5 regulatory subunit-associated protein 2 (CDK5RAP2), a gene associated with primary microcephaly (Lancaster et al. Nature 2013). Briefly, an hiPSC line was electroporated using the ArciTect CRISPR-Cas9 ribonucleoprotein complex and cloned in mTeSR1 supplemented with CloneR. Stable hPSC clones were further characterized for karyotype and differentiation potential using

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the hPSC Genetic Analysis Kit and the STEMdiff Trilineage Differentiation Kit respectively. We generated clones harbouring CDK5RAP2 mutations in one allele (heterozygote) or two alleles (compound heterozygote). Stable clones were differentiated into cerebral organoids using the STEMdiff Human Cerebral Organoid Kit. Cerebral organoids generated from the compound heterozygote were ~25% smaller than control and heterozygote lines (n=4). Using RT-qPCR, day 18 organoids were found to have increased DCX and βIII tubulin, neuronal markers, and decreased PAX6 and SOX2, neural progenitor markers, in the compound heterozygote. Immunostaining of the cortical-like regions of day 18 organoids revealed disorganized structures and increased neurons in the ventricular zone-like region in the compound heterozygote. In summary, we developed a workflow to generate gene edited hPSC lines using the ArciTect system and provided a proof of principle method to model microcephaly.

1-C-109 *Identifying novel roles for Protein Disulfide Isomerase (PDI) in Amyotrophic Lateral Sclerosis (ALS)*

Sina Shadfar[1], Hamideh Shahheydari[1], Sonam Parakh[1], Angela Laird[1], Julie Atkin[1]

[1]Faculty of Medicine and Health Sciences, Macquarie University

Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration and death of motor neurons in the brain, brainstem and spinal cord. Previous studies in our group have established that protein disulphide isomerase (PDI) is protective against dysfunction to proteostasis induced by multiple mutant proteins in vitro in ALS. However, it remains unclear if PDI is also protective in vivo, or against other cellular mechanisms associated with ALS. In this study, we aimed to further define the protective properties of PDI in ALS. Expression of wild-type (WT) PDI in zebrafish expressing mutant superoxide dismutase (SOD1) A4V rescued motor impairment and axonopathy. Hence, these data reveal that PDI is protective against ALS-like phenotypes in vivo. Furthermore, studies in a motor neuron-like cell line, NSC-34, revealed that PDI was also protective against DNA damage, a mechanism that is becoming increasingly being implicated in ALS. In cells stressed with 13.5 μM etoposide for 30 minutes, significantly fewer p53 binding protein (53 BP1) and H2A histone X (γH2AX) foci were formed in cells expressing PDI compared to controls. Moreover, transient expression of PDI mRNA prevented DNA damage, indicated by upregulation of γH2AX, induced by H2O2 in the zebrafish model. These results provide valuable insights into the protective role of PDI in ALS, and they imply that PDI has a broader protective role than previously realised. This study therefore has implications for future therapeutic studies for PDI based on these proteins.

1-C-110 *Investigating the early decline of neural stem cells in a mouse model of Alzheimer's disease*

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Richard Harris[1], Bensun Fong[1], David Cook[1], Daniel Figeys[1], Ruth Slack[1]

[1]University of Ottawa

Neurogenesis is the generation of new neurons from a pool of neural stem cells (NSCs). This occurs in discrete areas of the human brain including the subgranular zone of the dentate gyrus, a region of the hippocampus responsible for cognition and memory. Yet, a decline in neurogenesis occurs with advanced aging and has been implicated in the cognitive decline associated with Alzheimer's disease (AD). Our goal is to characterize the mechanism of NSC depletion during AD progression. Using the 3xTg mouse model of AD, we examined the dentate gyrus using cryo-immunofluorescence microscopy and cresyl violet histological staining. We discovered a decline in the pool of proliferating Sox2-positive NSCs and Dcx-positive immature neuroblasts by 1 month of age. Anatomical measurements revealed a decrease in the volume of the dentate gyrus as early as postnatal day 7 and a decrease in the volume of the hippocampus proper by 3 months of age. These observations suggest that NSC depletion in 3xTg mice occurs at a very early age and may be a contributing factor to the decreased volume of the hippocampus and cognitive decline apparent at later ages. A combination of bulk RNA-sequencing from isolated CD15-positive NSCs and single-cell RNA-sequencing from tamoxifen-induced NSCs using a Nestin-driven promoter has revealed mitochondria-centric gene-regulatory pathways that contribute to NSC depletion. These results elucidate the molecular mechanisms that govern NSC fate decisions in the AD brain and may reveal novel therapies for promoting regeneration in this neurodegenerative disease.

1-C-111 *Initiating a neuronal reprogramming strategy targeting the motor cortex in a mouse model of ALS*

EunJee Park[1], Kelly Coultes[2], Carol Schuurmans[2], Isabelle Aubert[2], Janice Robertson[1]

[1]University of Toronto, [2]Sunnybrook Research Institute

Amyotrophic lateral sclerosis (ALS) is a terminal neurodegenerative disease that results in a loss of motor neurons in the brain and spinal cord, leading to a deterioration of motor function and ultimately culminating in death. Currently there are no effective therapies for ALS. My goal is to develop novel therapeutic strategies that replace or prevent the degeneration of upper motor neurons (UMNs) in the motor cortex of the brain. Our brain-centric approach is predicated on the postulated dying forward model, which suggests that UMN pathology precedes lower motor neuron (LMN) loss in the brainstem and spinal cord. Our hypothesis is that targeting ALS disease pathology in UMNs will delay or even prevent the progression of ALS to LMNs. For this purpose, we use SOD1G93A transgenic mice, an ALS model. We are characterizing neuronal loss and astrocyte activation in the neocortex of SOD1G93A mice. We are also evaluating the therapeutic efficacy of replacing lost UMNs on ALS disease progression using in vivo neuronal reprogramming, converting toxic astrocytes to new neurons. We showed that Ascl1 promotes the

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differentiation of UMN layer V neurons in the embryo. Now we have used AAV2/8-GFAPp-Ascl1-mCherry to drive Ascl1 expression in astrocytes in SOD1G93A mice. We have shown that mCherry cells convert to a neuronal identity based on the expression of NeuN. Future studies will compare the efficacy of Ascl1 versus other neuronal determination factors in neuronal conversion in this model system, and the effects of this conversion on disease progression.

1-C-112 *Optic nerve injury induces necroptosis in retinal ganglion cells*

Philippe D'Onofrio[1], Alireza Shabanzadeh[1], Brian Choi[1], Paulo Koeberle[1]

[1]University of Toronto

Purpose: Necroptosis is a death mechanism that has been implicated in several neurodegenerative diseases. We investigated if it is involved in retinal ganglion cell (RGC) death after optic nerve axotomy and if it prevents neurite regeneration after optic nerve crush. As such, we administered inhibitors to the 3 main necroptosis signaling factors: Receptor Interacting Protein kinase (RIP) 1, RIP3, and Mixed Lineage Kinase domain-Like protein (MLKL). Methods: Optic nerve transection and optic nerve crush were used to study RGC survival and regeneration, respectively. Treatments were administered into the cut end of the optic nerve or via intravitreal injection. RGC survival and neurite regeneration was assessed by immunohistochemistry, confocal microscopy, and cell counting; peptide levels and localization were assessed by western blot and immunohistochemistry, respectively. Results: RIP1, RIP3, or MLKL inhibition increased RGC survival when administered at 3 days post-axotomy. RIP3 levels increased between 3-7 post-axotomy and RIP3 and MLKL were localized to RGCs at 2 to 7 days post-axotomy. Inhibition of RIP1, RIP3, or MLKL increased RGC neurite regeneration at 21 days post-crush. Conclusions: Inhibition of RIP1, RIP3, and MLKL present useful targets to rescue RGCs. RGC survival was improved when treatment was administered at 3 days post-axotomy, when apoptosis is also initiated. As such, this suggests that apoptosis and necroptosis are activated concurrently and that simultaneously targeting both presents a promising avenue for future research.

1-C-113 *Anxiety in Parkinson's disease: the role of the locus coeruleus-stress circuitry*

Mohsen Seifi[1], Jerome Swinny[1]

[1]University of Portsmouth

Introduction: In addition to the cardinal motor deficits, Parkinson's patients also present with non-motor symptoms which significantly magnify the disease and care burden. One such prominent non-motor symptom is anxiety. Anxiety is inextricably linked to maladaptive fear or stress responses. A key modulator of our behavioural responses to stress is the noradrenergic nucleus

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locus coeruleus (LC). We currently do not know how LC function changes in the early stages of Parkinson's, and whether such changes contribute to anxiety in patients. Therefore, the overall aims of the project are to characterise the molecular, physiological and behavioural correlates of the LC-stress pathways in a Parkinson's mouse model that overexpresses human alpha-synuclein (SNCA) at disease-relevant levels. Methods: 1) Animal models of stress and anxiety; 2) ELISA, immunohistochemistry and confocal microscopy; 3) patch-clamp recordings of spontaneous LC neuronal activity. Results: SNCA-overexpressing mice exhibited a hyper-stress phenotype, demonstrated by a significantly elevated blood cortisol concentration. They also displayed an anxiogenic-like behavioural phenotype in the light-dark box assay. This was accompanied by an increased spontaneous firing rate of LC neurons and a decrease in the expression of GABAA and glycine receptors in these neurons. Conclusion: The study provides unique insights into the potential underlying mechanisms of anxiety in Parkinson's, namely heightened LC excitability and an exaggerated response to stressors.

1-C-114 *Molecular and functional characterisation of Alzheimer's disease (AD) pathology in the mouse intestine: implications for novel therapies to treat intestinal dysfunction in AD*

Adina Gibbard[1], Mohsen Seifi[1], Jerome Swinny[1]

[1]University of Portsmouth

Background: In addition to devastating effects on brain function, Alzheimer's disease (AD) also alters functioning of the enteric nervous system (ENS), a branch of the peripheral nervous system that regulates gastrointestinal (GI) function. As a result, patients suffer from symptoms primarily of GI origin, such as constipation or faecal incontinence, thereby magnifying the disease burden. We know that AD pathology exists within the ENS. However, we do not know how such pathology impacts on ENS function and that of the GI tract, notably, motility. The aims of the project were to characterise AD induced molecular and functional changes in ENS neurotransmitter machinery and GI motility respectively, in the transgenic (TG) APP/PSEN1 mouse model of AD. Objectives: 1.Does AD pathology alter the expression of neurotransmitter systems in the GI tract? 2.How do AD-induced GI neurochemical changes impact on motility? Methods: 1) Neurotransmitter-receptor expression analysis using quantitative PCR and immunohistochemistry; 2) spontaneous and pharmacologically-evoked intestinal muscle contractility using isometric tension recordings in an organ bath. Results: AD pathology induced an array of changes in neurotransmitter systems integral to GI motility, at the mRNA and protein levels. Furthermore, colonic TG tissue exhibited a hypercontractility phenotype. Conclusion: The study reveals molecular and functional changes in the GI system as a result of AD pathology, thereby identifying potential molecular targets for treating the associated symptoms in patients.

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1-C-115 *Regulating PTEN recruitment reduces CNS Ischemic and Traumatic injury*

Alireza Shabanzadeh Pirsaraei[1], Philippe M. D'Onofrio[1], Philippe M. Monnier[2], Paulo D. Koeberle[1]

[1]University of Toronto, [2]University of Toronto, Krembil Research Institute

Phosphatase and Tensin homologue (PTEN) regulates apoptosis and axonal growth in the developing and adult central nervous system (CNS). Here, we show that this pathway plays a critical role in regulating neuronal apoptosis and regeneration after traumatic CNS injury and stroke, highlighted by the findings that antagonizing the PDZ motif-interactions of PTEN have therapeutic applicability for these indications. Interestingly, the death-inducing function of PTEN following ischemic insult depends on a PDZ domain interaction with MAGI-2 and MAST205, which recruit PTEN to the plasma membrane and stabilize its interaction with PIP3. Treatments with a peptide that prevents PTEN association with MAGI-2 or MAST205 increased neuronal survival in several in vitro stroke models. In rats, a pro-survival effect was also observed in a model of ocular ischemia as well as after middle cerebral artery occlusion (MCAO) and optic nerve transection. PTEN peptide treatment also improved neuronal survival, regeneration, and the complexity of the neuronal network following ischemic or traumatic CNS injury. Furthermore, the PTEN peptide promoted significant functional improvement after middle cerebral artery occlusion or ophthalmic artery ligation. These findings show that peptide-based targeting of c-terminal PTEN PDZ interactions has therapeutic potential for insults of the CNS including trauma and stroke. Keywords: PTEN, apoptosis, trauma, stroke, regeneration

1-C-116 *Delayed post-traumatic neuronal death in the developing hippocampus*

Trevor Balena[1], Lauren Lau[1], Negah Rahmati[1], Kyle Lillis[1], Kevin Staley[1]

[1]Massachusetts General Hospital

Delayed neuronal death (DND) is of interest as a means to explain clinical deterioration after acute brain injury. However, mechanisms underlying DND and its relationship to apoptosis remain poorly understood. We evaluated the death of neurons in a chronically epileptic in vitro preparation in which multiphoton microscopy could be performed over a period of several days. Organotypic hippocampal slice cultures were made from wild-type C57BL/6J mice, and imaged with transgenic fluorophores as well as the Na+ dye SBFI-AM. The first detectable event was loss of participation in network activity and mild, sustained elevation of cytoplasmic Ca2+. The second stage was marked by activation of caspases and the loss of fluorescence of transgenic fluorophores. In the third stage, neurons admitted AM dyes including SBFI-AM. The fourth stage was marked by steady increases in cytoplasmic Na+ to concentrations approaching that of the extracellular solution. During this stage, cytoplasmic membrane damage, retraction of dendrites and axons, and condensation of nuclear chromatin became progressively evident. Throughout the fourth stage, glycolysis and mitochondrial respiration and ATP production, sodium transport via Na+/K+

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ATPases, and secondary transport including cation-Cl- cotransport and Na+/Ca2+ exchange were all ongoing. Key events in the fifth and final stage included microglial engulfment, sharp rises in Na+ and Ca2+ concentrations, and terminal cell shrinkage. Overall, we describe here a new in vitro model of delayed neuronal cell death in the developing hippocampus.

1-C-117 *Perturbations in nuclear-cytoplasmic transport on stress granule dynamics: implications in ALS.*

Joseph-Patrick Clarke[1], Jocelyn Mauna[1], Christopher Donnelly[1]

[1]University of Pittsburgh

Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are progressive, fatal neurological diseases caused by the loss of cortical and/or motor neurons in the central nervous system (CNS). A molecular similarity between both neurological diseases is the observed cytoplasmic aggregation of the RNA-binding proteins TDP-43 or FUS in affected CNS tissue. In healthy cells, these proteins are predominantly nuclear, trafficking into and out of the cytoplasm, while in disease, they are absent from the nucleus and form cytoplasmic aggregates through currently unknown mechanisms. Current hypotheses suggest that either perturbations in nuclear-cytoplasmic trafficking, or impaired homeostasis of cell stress activated cytoplasmic granules, called stress granules (SGs), may promote the seeding of TDP-43 and/or FUS aggregation in disease, and thus may promote disease progression. We investigated whether perturbation of nuclear-cytoplasmic trafficking causes impaired SG dynamics, and contingent upon this pathway being integrated, could seed TDP-43 cytoplasmic aggregation. Additionally, we developed a novel method employing light-induced, photoreceptor protein clustering to seed the core protein components of SGs to assess whether impaired SG dynamics occurs in the absence of cytotoxic stressors, as continuous stress treatment prevents the study of prolonged or repetitive SG formation in the induction of ALS/FTD neuropathology. The overall goal of this work is to further study the molecular pathology underlying ALS and FTD.

1-C-118 *Do patterns matter: The effects of phasic vs. tonic locus coeruleus activation on similar odor discrimination learning*

Abhinaba Ghosh[1], Faghihe Massaeli[1], Sarah Torraville[1], Vanessa Strong[1], Carolyn Harley[1], Xihua Chen[1], Qi Yuan[1]

[1]Memorial University of Newfoundland

Noradrenergic neurons in the locus coeruleus (LC) exhibit phasic and tonic spiking patterns in vivo. While a phasic spiking pattern is correlated with focused attention, cortical encoding of

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salience, and high utility, a tonic pattern is associated with stress, distractibility, and exploratory behavior. Our previous work has shown that LC mediated norepinephrine release in the piriform cortex is necessary for pattern separation-dependent difficult odor discrimination learning. However, whether, and how, tonic and phasic LC spiking patterns differentially modulate odor discrimination learning is not known. Here we answer this question by optogenetic stimulation of the LC in TH-CRE rats transfected with AAV8-Ef1a-DIO-eChR2 (H134R)-EYFP, locally infused to the LC. Control rats are infused with an AAV8-Ef1a-DIO- EYFP. Three weeks following infusion, optical cannulas are implanted bilaterally in the LC and, a week later, olfactory discrimination learning ability is tested in a food-retrieval paradigm. Light activation is given to both ChR2 rats and control rats during the associative odor training. Preliminary results show that acute 10 Hz phasic stimulation of the LC (10s on, 20s off) accelerated difficult odor discrimination learning. LC ChR2 expressing rats with 10 Hz phasic activation demonstrated enhanced learning, with fewer training days required to reach successful learning criterion than the control rats. We are currently testing the effect of tonic LC patterns on odor discrimination learning.

1-C-119 *Temporal self-appraisal in developmental amnesia*

Julia Halilova[1], Donna Rose Addis[2], R. Shayna Rosenbaum[1]

[1]York University, [2]Rotman Research Institute, Baycrest Hospital

According to temporal self-appraisal theory, people tend to evaluate themselves in the past in a way that makes them feel good about themselves in the present (Wilson & Ross, 2001). In line with this theory, studies have shown that neurologically healthy individuals tend to believe that their personality has changed more in a certain period of time in the past than it will change in the same period of time in the future. Here we investigated whether episodic memory plays a role in one's ability to adjust their appraisals of themselves in the past and future in order to maintain a favourable view of self in the present. We tested a developmental amnesic person with episodic memory impairment (H.C.) and a group of age-matched controls on tasks assessing the Big Five personality traits in the present, in the past (5 years ago), and in the future (5 years from now). Consistent with previous research, we found that controls believe that their personality has changed significantly more in the past 5 years than it will change in the next 5 years. Patient H.C. shows a similar pattern of results. No significant differences in absolute values of change from past to present and from present to future were found between H.C. and controls. The findings suggest that temporal self-appraisal does not require one to revisit specific unique experiences in episodic memory, but, instead, might be supported by a personal schema that emerges from multiple experiences over time.

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1-C-120 *Degeneration of the nigro-striatal dopaminergic neurons in a rat model of chronic hyperglycemia.*

Maria-Grazia Martinoli[1], Justine Renaud[1], Jimmy Bealieu[1], Valentina Bassareo[1], AnnaLisa Pinna[2], Nicola Simola[2]

[1]Université du Québec, [2]University of Cagliari

Study's objective: The aim of this study was to caracterize the effects of long-term hyperglyemia in dopaminergic pathways, the nigrostriatal motor pathway and the reward-associated mesocorticolimbic pathway. Our team already established that elevated levels of glucose lead to oxidative stress and apoptosis in cultivated dopaminegic neurons and several other studies report dopaminergic alterations in diabetes or acute hyperglycemia. Methods: in a nicotinamide-streptozotocin rat model of hyperglycemia, the nigrostriatal motor pathway and the reward-associated mesocorticolimbic pathway were specifically investigated by biochemical techniques. Behavioural alterations were assessed in a series of tasks designed to uncover motor deficits in rodent models of Parkinson's disease (PD). Results: neuronal and glia alterations were evaluated 3 and 6 months after hyperglycemia. Our results demonstrate preferential degeneration of the nigrostriatal pathway associated with astrogliosis and loss of microglial cell after 6 months. Long-term hyperglycemic rats manifested signs of bradykinesia and gait disturbances reminescents of parkinsonism motor impairment. Interestingly, motor deficits and dampened dorsostriatal dopamine release were apparent before neurodegeneration could be discerned, suggesting possible functional impairments of the nigrostriatal pathway before of neuronal death. Conclusion: these results provide refreshing insights on the higher occurrence of PD in diabetic patients.

1-C-121 *Susceptibility to micro-circulatory obstructions can predict brain region specific vessel loss with aging*

Ben Schager[1], Craig Brown[1]

[1]University of Victoria

The loss of microvessels in the aging brain has been reported in virtually all animals. Despite this, there remain important questions regarding whether there are brain-region specific vulnerabilities to vessel loss and what mechanisms could account for this. Recent data from our lab indicate that cortical microvessels are prone to spontaneous, long-lasting obstructions that can lead to vessel pruning. Here we rigorously tested whether there are regional differences in vessel loss with aging and whether rates of capillary obstructions in different areas can predict the magnitude of vessel loss. Using fluorescent dyes to label the vasculature, we quantified vessel density in young (2-4 month) and aged (18-22 month) mice. Our data indicate that microvessel loss was highly variable

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across 15 brain regions, with loss in white matter more pronounced than in cortical and subcortical grey matter. Further, brain regions supplied by the anterior cerebral artery (ACA) were more vulnerable to vessel loss than those supplied by the MCA or PCA. In order to explain regional patterns of vessel loss, we injected 4µm fluorescent microspheres (i.v.) to model naturally occurring capillary obstructions and imaged their distribution 3 days later. We discovered that those brain regions with a higher density of obstructions were more likely to show vessel loss with aging and vice versa. These findings indicate that age-related vessel loss is not uniform, but rather region specific and can be predicted by regional susceptibilities to micro-circulatory obstructions.

1-C-122 *Age-related changes in the free water compartments of grey and white matter are associated with depression and mild cognitive impairment*

John A Anderson[1], Benoit Mulsant[2], Nathan Herrmann[2], Linda Mah[2], Alastair Flint[2], Corrine Fischer[2], Bruce Pollock[2], Tarek Rajji[2], Aristotle Voineskos[2]

[1]CAMH, [2]University of Toronto

Objective: Late-life depression (LLD) escalates risk for Alzheimer's, but the link between these disorders is unclear. Both disorders are independently associated with neuroinflammation. Our objective was to use free-water (FW) which may index neuroinflammation in grey (GM) and white matter (WM). We hypothesized diagnostic severity would predict greater age-related atrophy. Methods: We acquired multishell scans for 276 participants from 4 groups (Healthy controls (HC), n=22; late-life depression (LLD), n =49 ; mild cognitive impairment (MCI), n=127 ; LLD+MCI, n=78). Using the NODDI algorithm, we estimated FW properties in GM and WM. Multivariate PLS modeled how FW covaried with age by group. Results: In GM, 3 significant latent variables (LV's) explained 92% of the covariance (CoV). The first LV, $p < 0.0001$, showed a stronger age-free-water coupling in HC ($r = 0.94$) than the other groups (all $r < 0.65$). For LV2, $p = 0.046$, age predicted FW in left caudate in clinical groups, $rs > 0.73$, (but not HC). LV3, $p = 0.028$, showed age coupled FW in right caudate differentiated MCI status from HC and LLD. The first WM LV, $p < 0.0001$, 74% CoV echoed the results of the first GM LV. Conclusion: We used FW to characterize spatially distinct patterns of age-related atrophy that distinguished HC from clinical groups. Furthermore, bilateral caudate nuclei appear disproportionately vulnerable to MCI and this characterizes LLD to a lesser degree. These findings have potential ties to frontostriatal circuits governing behavior and depression as well as iron accumulation in subcortical regions.

D - Sensory and motor systems

1-D-123 *Implicit and explicit learning in response to novel arm dynamics*

Julia Zdybal[1], Rodrigo Maeda[1], Andrew Pruszynski[1]

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[1]University of Western Ontario

Generating pure elbow movements requires contracting muscles at both the shoulder and the elbow to counter interaction torques that arise at the shoulder when the forearm rotates (ie. arm dynamics). Previous work has shown that subjects learn to reduce their shoulder muscle activity if the same elbow movement is performed with the shoulder fixed, altering the arm's dynamics (Maeda et al., 2018). However, this learning occurs slowly and is incomplete. Here we investigated whether and how implicit and explicit learning systems contribute to this type of learning and how these learning systems interact. Human participants (n=55) performed voluntary elbow reaches using a robotic exoskeleton that permits shoulder and elbow rotation in the horizontal plane. First, participants did the task with the shoulder free to move (baseline). We then locked the shoulder joint and subjects repeated the same elbow reaches (adaptation). Lastly, we unlocked the shoulder joint and subjects again made elbow reaches (post). One group performed this protocol with no instructions given about what to do after the shoulder was locked (implicit). A second group performed this protocol with visual feedback about their shoulder muscle activity and was instructed to reduce shoulder muscle activity to zero (explicit). We found that the rate and magnitude of learning was not significantly different between the implicit and explicit groups suggesting that learning new arm dynamics, unlike other motor learning paradigms, is a relatively automatic process.

1-D-124 *Responses to infant vocalizations in oxytocin neurons*

Silvana Valtcheva[1], Robert Froemke[1]

[1]NYU School of Medicine

Healthy maternal sensitivity is characterized by the ability to reliably interpret and respond to infant signals, thus initiating appropriate caregiving responses. Motherhood is a dramatic natural experience but little is known about the specific circuits and neural mechanisms supporting the recognition of different infant cues. Recent studies from our lab (Marlin et al., 2015) showed that oxytocin promotes long-term plasticity of neural responses to infant sounds in mouse auditory cortex in vivo. Release of oxytocin from the paraventricular nucleus (PVN) of the hypothalamus might help induce recognition of distinct infant cues but it remains unknown which sensory stimuli activate oxytocin neurons. Here we performed in vivo cell-attached and whole-cell recordings from PVN neurons in awake mice. We used channelrhodopsin-assisted patching (Munoz et al. 2014) to record from optically-identified oxytocin neurons in maternal mice. We found that oxytocin neurons reliably respond to pup calls but not to behaviorally-irrelevant pure tones. Interestingly, repeated presentation of pup calls induced a gradual increase in tonic firing of individual oxytocin neurons. Using rabies virus tracing, we identified inputs which may drive auditory responses in oxytocin neurons. Finally, we mapped populations of PVN neurons that are activated by pup calls or suckling via c-fos and if these neurons were magno- or parvocellular.

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Our data suggest that oxytocin neurons differentially integrate auditory and somatosensory information which may be critical for the recognition of different infant cues.

1-D-125 *Role of TASK channels at the hypoglossal motor nucleus in modulating motor output*

Patrick Gurges[1], Hattie Liu[1], Richard Horner[1]

[1]University of Toronto

Obstructive sleep apnea (OSA) is a common and serious breathing disorder that occurs exclusively during sleep due to reduced tongue muscle tone. The latter is due to withdrawal of excitatory inputs (e.g., serotonin, 5-HT) to the hypoglossal motor nucleus (HMN) from wakefulness to sleep. 5-HT and several other wake-active neurotransmitters with inputs to the HMN all inhibit TWIK-Related Acid-Sensitive Potassium (K+) leak (TASK-1/3) channels on hypoglossal motoneurons in-vitro, leading to increased motor activity. We hypothesize that inhibition of hypoglossal TASK channels will increase tongue muscle activity in-vivo, and modulate the responses to applied 5-HT. We microperfused the HMN of isoflurane anesthetized rats with TASK channel inhibitors: (i) doxapram (75uM, n=9), (ii) A1899 (25uM, n=9), (iii) ML365 (25uM, n=9), (iv) acidified artificial cerebrospinal fluid (ASCF, pH=6.25, n=9); or (v) the TASK channel activator terbinafine (50uM, n=9). In each study the interventions were performed with or without co-applied 5-HT (10mM). Microperfusion of 5-HT alone into the HMN increased tongue muscle tone (202.8 +/- 45.9%, each $P<0.001$). Application of the TASK channel activators or inhibitor to the HMN did not change baseline tongue muscle tone (each $P>0.716$), nor the response to applied 5-HT (each $P>0.127$). These findings suggest a minimal role of TASK channels at the HMN in modulating tongue motor activity in-vivo, and that their targeted modulation would not be expected to increase tongue motor tone as a potential pharmacotherapy for OSA.

1-D-126 *Audiovisual multisensory processing in university aged adults with attention-deficit/hyperactivity disorder*

Heather McCracken[1], Bernadette Murphy[1], James Burkitt[1], Cheryl Glazebrook[2], Paul Yielder[3]

[1]University of Ontario Institute of Technology (UOIT), [2]University of Manitoba, [3]University of Ontario Institute of Technology

This work assessed audiovisual sensory processing in the form of multisensory integration (MSI) in a university aged sample with Attention-Deficit/Hyperactivity Disorder (ADHD). The integration of sensory inputs that are presented simultaneously is known as MSI (Paraskevopoulos & Herholz, 2013). Individuals with ADHD have behavioural and neurological characteristics that may

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influence MSI when in sensory rich environments (Biederman et al., 2004; Proal et al., 2011). This study consisted of a two-alternative forced-choice discrimination task, emphasizing response time and accuracy, while continuous whole-head electroencephalography (EEG) was recorded. Stimuli included a visual unisensory (red, blue, or green filled circle), auditory unisensory (female verbalization), and a semantically congruent audiovisual multisensory stimulus. The ADHD group had shorter response times to each stimulus ($p = 0.048$) while both groups responded most accurately to the auditory unisensory stimulus compared to the visual unisensory stimulus ($p < 0.001$). The ADHD group had violation of the race model in the first ($p = 0.028$) and third ($p = 0.016$) quantiles. EEG analyses demonstrated that MSI occurred in both groups ($p = 0.046$) from 110-130 ms post-stimulus onset over parietal occipital regions. However, the ADHD group had greater MSI at this latency and brain region ($p = 0.033$). This is the first research to suggest that those with a diagnosis of ADHD integrate audiovisual inputs differently than neurotypical controls. This may be related to neurological characteristics of those with ADHD.

1-D-127 *How does closed-loop feedback generate neural and behavioral responses to weak sensory input?*

Chelsea Kim[1], Maurice Chacron[1]

[1]McGill University

Understanding how the brain decodes sensory information to give rise to behaviour remains a pivotal problem in systems neuroscience. Across various sensory modalities (e.g. auditory, visual), weak and slow amplitude modulations (AMs) of natural stimuli have shown to carry behaviourally relevant information. Unfortunately, it is unclear how such information is decoded by the brain to evoke perception and behaviour. A recent study in our lab has unveiled a novel function of feedback in the electrosensory system, in that it generates both neural and perceptual responses to naturalistic weak AM stimuli. More specifically, the descending projections are necessary to transform a temporal code to a rate code that is then decoded downstream to generate perception and behaviour. Here we used a combination of computational and experimental approaches to better understand the mechanisms underlying this transformation. Our experimental evidence shows that midbrain neurons responded to the ascending temporal code with a rate code, thereby transforming it. Furthermore, our simplified model predicts that this conversion requires a sigmoidal non-linearity. Overall, these results provide an elegant mechanism by which feedback pathways generate neural and behavioural responses to weak sensory input, which is likely to generalize across systems and species.

1-D-128 *Changes in connectivity to DI3 interneurons and spinal motoneurons following spinal cord injury in mice*

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Sara Goltash[1], Fariba Sharmin[1], Tuan Bui[1]

[1]University of Ottawa

Unlike humans, many mammals show the ability to recover some form of locomotor function following serious spinal cord injury. Understanding the mechanisms that allow mammalian spinal cords to recover from neurotrauma to generate locomotor activity could inform future therapies aimed at producing persistent recovery of locomotor function in human spinal cord injury patients. Previous work identified dI3 interneurons as a spinal neuron population central in the recovery of locomotor function in spinalized mice. We seek to determine the changes in the circuitry of dI3 interneurons following spinalization in adult mice. Transgenic Isl1:YFP mice underwent complete transection at the T9-T11 levels. They were subsequently trained on a treadmill to recover locomotor function. At various time points of recovery following surgery, we examined changes in several key circuits involving di3 interneurons and spinal motoneurons. More specifically, we examined changes in 1) Sensory inputs from proprioceptive and cutaneous afferents, 2) Presynaptic inhibition of sensory inputs, 3) Excitatory glutamatergic synapses from spinal neurons, 4) dI3 interneuron to motoneuron direct inputs. Our preliminary results suggest that there are reductions in central and sensory inputs to both dI3 interneurons and spinal motoneurons immediately following spinal cord injury. Some of these losses were partially recovered during treadmill training. These results suggest remodeling of spinal circuits during training as a form of adaptation to promote locomotor recovery.

1-D-129 *Visual discrimination between complex objects gates early excitatory oculomotor projections during saccade task*

Devin Kehoe[1], Jennifer Lewis[2], Mazyar Fallah[1]

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

Recently, Kehoe and Fallah (2017) developed a non-invasive technique to measure the time course of excitatory and inhibitory activity encoding a peripheral distractor in which human saccade curvature is modeled as a continuous function of saccade-distractor onset asynchrony (SDOA): the time between the transient onset of a task irrelevant distractor and the initiation of a saccade to a target. Here, we used the SDOA technique to investigate how varying the degrees of visual similarity between a distractor and the target affect the time course of excitatory and inhibitory distractor-related processing while human observers (N = 35) performed a discrimination saccade task for pairs of complicated, novel objects. Consistent with differences in target-distractor discrimination time between similar/dissimilar distractors observed in SC (Shen & Paré, 2012) and FEF (Sato et al., 2003) neurons, we observed that the latency of the distractor-related inhibitory response was 40-60 ms later for the high similarity distractor than for the intermediate/low similarity distractors. Interestingly, we also observed that the latency of the initial

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rapid excitatory response was ~60 ms longer for the high similarity distractor than for the intermediate/low similarity distractors, which suggests that the early excitatory response observed during oculomotor target selection processing does encode top-down information under certain task-related conditions.

1-D-130 *Task-specific V3 spinal interneuron circuit modules revealed through distinct subpopulation topographies*

Dylan Deska-Gauthier[1]

[1]Dalhousie University

Animals exhibit a wide range of locomotor behaviours that emerge from the coordinated activity of circuits in the spinal cord directing patterned motor output. While spinal interneurons (INs) are known to play an essential role in establishing precise temporal patterns of muscle contraction, the principles governing recruitment of INs across different behaviours remain elusive. Here, we combine computational models to systematically analyze task-specific c-fos expression within the cardinal V3 IN population in the mouse spinal cord. Our analysis reveals a topographic arrangement of V3 INs into functionally distinct modular domains. Furthermore, we uncover molecularly discrete Nr3b3+, Onecut2+ and Prox1+ V3 IN subpopulation clusters that form unique connectivities, and most notably, differentially assemble within distinct V3 modular domains. Thus, our current work indicates that developmentally and genetically discrete IN subpopulations are the building blocks of topographically clustered spinal circuits engaged in different locomotor tasks.

1-D-131 *Immunohistochemical phenotyping of sensory neurons associated with sympathetic plexuses in the mouse trigeminal ganglia*

Hanin Alsaadi[1], Jacob Peller[1], Nader Ghasemlou[1], Michael Kawaja[1]

[1]Queen's University

Following peripheral nerve injury, postganglionic sympathetic axons sprout into affected sensory ganglia and form perineuronal plexuses around a subpopulation of primary sensory neurons. These sympathetic basket-like structures have been shown to play an important role in the development and maintenance of chronic pain. In this study, we sought to determine a more precise phenotype trigeminal ganglia neurons surrounded by sympathetic plexuses. Here we utilized mice that express nerve growth factor (NGF) under the control of glial fibrillary acidic protein promoter, as these mice display the spontaneous formation of sympathetic baskets in sensory ganglia (i.e., in the absence of nerve injury). Preliminary immunostaining results show that

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the vast majority of those sensory neuronal cell bodies surrounded by sympathetic plexuses in the trigeminal ganglia are immunopositive for 1)the NGF receptor trkA, 2)a second NGF receptor p75, 3)calcitonin gene-related peptide, 4)neurofilament heavy chain (NF200),and 5)P2X purinoceptor 3. These same sensory neurons with sympathetic basket lack immunostaining for NGF receptor trkB, isolectin B4, substance P, TRPV1, Aquaporin, and ASIC3. These results reveal that the nociceptive sensory neurons surrounded by sympathetic plexuses are a subpopulation of NGF-sensitive neurons consistent with PEP2 classification in Usoskin et al.(2015). This study sheds light on the mechanisms that provide specificity in the formation of sympathetic plexuses. This knowledge is imperative for developing targeted interventions for sympathetically maintained pain

1-D-132 *Insulin-like growth factor-1 augments mitochondrial function through AMPK to drive axonal repair and protect from sensory neuropathy in type 1 diabetes*

Mohamad-Reza Aghanoori[1]

[1]University of Manitoba

Diabetic neuropathy (DN) affects approximately half of diabetic patients leading to significant morbidity. We hypothesized that sub-optimal insulin-like growth factor 1 (IGF-1) signaling in diabetes drives loss of AMPK activity and mitochondrial function, both contributing to development of DN. Age-matched control and streptozotocin (STZ)-induced type 1 diabetic rats with/without IGF-1 therapy were used for in vivo studies. For in vitro studies, DRG neurons were used. Dysregulation of mRNAs for IGF-1, AMPKa2, ATP5a1 (subunit of ATPase) and PGC-1ß occurred in DRG of diabetic vs. control rats. IGF-1 up-regulated mRNA levels of these genes in cultured DRGs from control or diabetic rats. IGF-1 treatment of DRG cultures significantly ($P<0.05$) increased phosphorylation of Akt, P70S6K and AMPK. Mitochondrial gene expression and oxygen consumption rate, ATP production, mtDNA/nDNA ratio and neurite outgrowth were augmented ($P<0.05$). AMPK inhibitor, Compound C, or AMPKa1-specific siRNA suppressed IGF-1 elevation of mitochondrial function, mtDNA and neurite outgrowth. Diabetic rodents treated with IGF-1 exhibited reversal of thermal hypoalgesia and the deficit in corneal nerve profiles. In diabetic rats, IGF-1 elevated the levels of AMPK and P70S6K phosphorylation, raised Complex IV-MTCO1 and Complex V-ATP5a protein expression, and restored the enzyme activities of Complex IV and I in the DRG. IGF-1 prevented TCA metabolite build-up in nerve. In DRG neuron cultures IGF-1 signals via AMPK to elevate mitochondrial function to protect from distal dying-back of fibers in DN.

1-D-133 *Endogenous IGF-1 in dorsal root ganglia is expressed by sensory neurons, drives neurite outgrowth and is suppressed in the diabetic state*

Mohamad-Reza Aghanoori[1], Paul Fernyhough[1]

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[1]University of Manitoba

IGF-1 is a pleiotropic factor with a wide range of action on the nervous system and its levels decline with age. Recently, IGF-1 has been used for treatment of neurodegenerative disorders such as ALS. We hypothesized that impaired autocrine/paracrine IGF-1 in dorsal root ganglia (DRGs) is a contributing factor to progressive neurodegeneration and impaired nerve regeneration in diabetic neuropathy. DRG neuron cultures and sections/tissues from age-matched control or streptozotocin (STZ)-induced type 1 diabetic rats were used in this study. IGF-1 protein and mRNA levels in liver and DRG tissues were significantly ($P<0.05$) lower in type 1 diabetic rats vs control rats. DRG neurons derived from control rats released significantly ($P<0.05$) higher amount of IGF-1 in the media when compared to diabetic rats. Hyperglycemic conditions suppressed IGF-1 mRNA levels in cultured DRG neurons after 2 days. This inhibitory effect was relieved by IGF-1 treatment or using the sorbinol dehydrogenase inhibitor, Sorbinil. IGF-1 mRNA was primarily expressed in neurons of the DRG rather than in glial cells or sciatic nerve tissue determined by RNA-FISH and Northern blot analysis. In growth factor-free media, IGF-1 neutralizing antibody downregulated IGF-1 receptor and Akt S473 phosphorylation, and lowered background neurite outgrowth in cultured DRGs. In conclusion, downregulated endogenous IGF-1 in DRG neurons in diabetes may contribute to pathogenesis of progressive distal dying back neurodegeneration and its up-regulation at the mRNA level may be a promising target for therapeutic purposes.

1-D-134 *Lionfish venom elicits pain predominantly through the activation of non-peptidergic nociceptors*

Stephanie Mouchbahani-Constance[1]

[1]McGill University

The lionfish (Pterois volitans) is a venomous invasive species found in the Caribbean and Northwestern Atlantic. It poses a growing health problem because of the increase in frequency of painful stings, for which no treatment or antidote exists. Understanding the venom's algogenic properties can help identify better treatment for these envenomations. In this study, we provide the first characterization of the pain and inflammation caused by lionfish venom and physiological, calcium imaging and electrophysiological testing. Intraplantar injections of the venom produce a significant increase in pain behaviour, as well as a marked increase in mechanical sensitivity for up to 24 hours after injection. The algogenic substance(s) are heat-labile peptides that cause neurogenic inflammation at the site of injection and induction of Fos and microglia activation in the superficial layers of the dorsal horn. Finally, calcium imaging and electrophysiology experiments show that the venom acts predominantly on nonpeptidergic, TRPV1-negative, nociceptors, a subset of neurons implicated in sensing mechanical pain. These data provide the

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first characterization of the pain and inflammation caused by lionfish venom, as well as the first insight into its possible cellular mechanism of action.

1-D-135 *Investigating the neural basis of pain sensitivity in fibromyalgia syndrome using functional magnetic resonance imaging: a pilot study*

Howard Warren[1], Patrick Stroman[1], Jocelyn Powers[1], Gabriela Ioachim[1]

[1]Queen's University

Chronic pain affects roughly 20% of the Canadian population, yet the causes are often difficult to diagnose, and treatments are often only marginally effective. To improve diagnosis and treatment quality, a better understanding of the neural mechanisms underlying chronic pain states is required. Recent evidence suggests that chronic pain may involve not only alterations in the "reactive" component of descending pain regulation, as shown in previous studies, but also the "continuous" component. To determine the role that these components play, we used functional magnetic resonance imaging (fMRI) to compare the neural responses to pain in two participant groups: healthy female controls and female participants with fibromyalgia syndrome (FMS), a chronic pain condition that affects 2-4% of the Canadian population. Each participant underwent two fMRI sessions so that both their brainstems/spinal cords and brains could be studied. During these imaging sessions, we administered a thermal stimulus to the palm of each participant's right hand to elicit a calibrated pain response. For comparison, interleaved fMRI runs were also acquired with no stimulus applied. Participants were informed of the study type (stimulation or no stimulation) one minute before the stimulus onset, in order to allow time for anticipation. Analyses of connectivity and temporal properties of BOLD responses across regions of the CNS known to be involved in pain processing demonstrate important differences in the continuous component of descending pain regulation between controls and participants with FMS.

1-D-136 *Spinal nociceptive projection neurons are defined by Phox2a expression*

Robert Brian Roome[1], Susana Sotocinal[2], Annie Dumouchel[1], Shima Rastegar-Pouyani[1], William Scott Thompson[1], Samuel Ferland[3], Cyril Bories[3], Yves de Koninck[3], Jeff Mogil[2], Marie Kmita[1], Artur Kania[1]

[1]Institut de Recherche Clinique de Montreal (IRCM), [2]McGill University, [3]Université Laval

The relay of nociceptive signals from spinal neuronal circuits to the brain remains poorly understood. Classical experiments demonstrate that spinal dorsal horn projection neurons relay such signals to the parabrachial nucleus, thalamus, periaqueductal gray and other brain regions. To directly study the specific function of these pathways, we generated the Phox2a:Cre transgenic

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mouse line expressing Cre recombinase from the Paired-like Homeobox 2a (Phox2a) locus which encodes a developmentally-expressed transcription factor. Phox2a:Cre labels neurons in Lamina I and V of the spinal cord exhibiting classical projection neuron morphology. At least 90% of Phox2a:Cre neurons are spinofugal projection neurons, demonstrated by retrograde tracing from supraspinal locations. Activation of spinal Phox2a:Cre neurons using chemogenetics produces nocifensive behaviours in the absence of noxious stimuli. Furthermore, optogenetic activation of their axonal termini in the parabrachial nucleus results in escape behaviours and conditioned place aversion. Together, our data indicate that Phox2a:Cre is a genetic handle of the spinal nociceptive projection neurons that comprise the anterolateral tract, possibly permitting the dissection of the emotive, discriminative, motor and homeostatic components of pain.

1-D-137 *Fast and accurate edge-orientation processing by synaptic integration across the population of first-order tactile neurons*

Etay Hay[1], J Andrew Pruszynski[2]

[1]Krembil Centre for Neuroinformatics, CAMH, [2]University of Western Ontario

Our ability to manipulate objects relies on tactile inputs from first-order neurons that innervate the glabrous skin of the hand. Each neuron innervates many mechanoreceptors and has spatially-complex receptive field. Recent studies show that humans can process tactile edge orientation with high acuity and speed during hand function. Here we provide insights about how synaptic integration across the population of first-order tactile neurons can account for the discrimination speed and acuity. We first derive spiking models of human first-order tactile neurons that fit and predict responses to moving edges with high accuracy. We then use the model neurons to simulate the population response to different edge orientations. Using machine learning, we show that synaptic integration across the first-order neuronal population could underlie human ability to process edge orientation with high acuity and speed. Moreover, we differentiate the roles of integrating AMPA inputs and NMDA inputs in refining the discrimination and maintaining robustness over longer timescales. Our results thus provide new insight into the computations occurring in the earliest stages of the human tactile processing pathway and how they may be critical for supporting hand function.

1-D-138 *Investigation of placebo modulation of pain responses in the healthy human brainstem and spinal cord by means of fMRI*

Patrick Stroman[1], Jocelyn Powers[1], Gabriela Ioachim[1], Howard Warren[1]

[1]Queen's University

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Pain is the net result of nociceptive input and emotional and cognitive factors, and is mediated by descending signaling from brainstem regions to regulate spinal cord neurons. The brainstem and spinal cord are thus likely to play an important role in the placebo effect; when pain is reduced as a result of a person expecting reduced pain. The aim of this study was to investigate placebo analgesia in healthy participants by means of functional MRI of the brainstem and spinal cord. Each participant was familiarized with study procedures and the temperature required to produce moderate heat pain on the hand. They were told that this temperature would be used for fMRI studies in the "High" condition, and the "Low" condition would be 1 °C lower. Participants experienced 5 fMRI runs of each condition, in random order. The paradigm consisted of 30 seconds of stimulation, preceded and followed by 2-minute long "baseline" periods. Participants were informed of the study condition and temperature, 1 minute before the stimulation period. However, the same temperature was applied in all runs to elicit the placebo effect in the Low condition. Ratings of pain intensity and unpleasantness demonstrated significant differences ($p < 0.001$) between the two conditions. On average, the expectation of the lower temperature reduced ratings by 6 points on 100-point scales. FMRI results demonstrated significant connectivity across brainstem and spinal cord regions, with differences between High and Low pain conditions. The results demonstrate neural processes underlying the placebo effect.

1-D-139 *Melanopsin-immunoreactive neurons in the fish retina*

Tareq Yousef[1], William Baldridge[1]

[1]Dalhousie University

Objective Melanopsin is expressed by every class of zebrafish retinal neuron (Davies et al., Cell Mol Life Sci 68:4115-32, 2011). We are determining which retinal neuron subtypes are melanopsin-immunoreactive (IR) in goldfish and zebrafish. Methods Retinas were processed for immunohistochemistry with 1) pas350 (Davies et al., 2011) or 2) opn4a, monoclonal antibodies for the opn4m-1 protein. To determine which melanopsin-IR neurons are associated with dopamine, ɣ-aminobutyric acid (GABA) or cholinergic neurons, tissue was double-labelled appropriately and imaged with confocal microscopy. Results Pas350 and opn4a labelled neurons in all retinal layers, including presumptive horizontal (HC), bipolar, amacrine (AC) and ganglion cells. We examined 131 TOH-IR dopaminergic interplexiform cells (DICs) finding no melanopsin-IR. TOH-IR puncta were found apposed to melanopsin-IR somas, and vice versa. GABA and opn4a co-labelling was found in HCs. A subset of GABAergic ACs, both in the goldfish inner nuclear (20%) and ganglion cell (70%) layers showed opn4a-IR. Similar co-labelling was found in zebrafish. Goldfish retina HC axon terminals (HATs) were melanopsin-IR. Finally, most zebrafish and goldfish ChAT-IR somas were melanopsin-IR. Conclusions Our work is consistent with the known ubiquity of melanopsin-IR in the zebrafish retina. DICs are not melanopsin-IR but melanopsin-IR cells may contact DICs and vice versa. Melanopsin-IR was found in presumptive

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GABAergic HCs, HATs, ACs, and cholinergic ACs. This work is funded by an NSERC to WHB and a Mathers to TY.

1-D-140 *Intermittent failure of spike propagation in primary afferent neurons*

Dhekra Al-Basha[1], Steven Prescott[2]

[1]The Hospital for Sick Children, [2]University of Toronto

Primary afferent neurons convey somatosensory information to the central nervous system. Low-threshold mechanoreceptors (LTMRs) are classified as slow-adapting (SA) if they spike repetitively during prolonged stimulation. They are further subclassified as type 1 or 2 based on the regularity of spiking. Recording extracellularly from LTMR somata in mice, we observed irregular- and regular-spiking units consistent with putative SA1 and SA2 LTMRs but a third set of "semi-regular" units did not fit cleanly into the existing classification scheme. Analysis of their spiking revealed integer-multiple-patterned (IMP) spiking, comprising of a fundamental interspike interval (ISI) and multiples thereof. IMP spiking was reproduced by randomly removing spikes from an otherwise regular spike train. We hypothesized that "skipped" spikes arise from either intermittent failure of spike initiation or propagation. Simulations in a conductance-based model neuron given constant input failed to reproduce IMP spiking, thus excluding intermittent failure of spike initiation as the mechanism. On the other hand, regular spiking (SA2) units exhibited IMP spiking during recovery from lidocaine application to the dorsal root ganglion, consistent with an increased probability of spike propagation failure at the T-junction during partial sodium channel blockade. In contrast, application of lidocaine to cutaneous terminals where spikes are initiated caused longer ISIs rather than IMP spiking. Thus, our data show that spike propagation in LTMRs intermittently fails near the soma.

1-D-141 *Learning and categorization of objects through haptic exploration*

Kyle Gauder[1], Daniel Goldreich[1]

[1]McMaster University

With haptic exploration--the active manipulation of objects to gather information through the tactile sensory system--the brain can seamlessly integrate features into whole percepts, learning the categorical and statistical structures of the world. The information processing that underlies this ability is poorly understood. One way to understand this process is through Bayesian inference--a probability framework for comparing hypotheses as information is gathered. This approach has seen success in vision and audition but has rarely been extended into haptics. Here we compare human performance against that of an optimal Bayesian observer. We created a set of 3D-printed

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polygons from which we defined two novel categories with overlapping feature distributions. Forty-five participants completed nine blocks of forty trials in one of three training regimens: 1) single-category exposure followed by testing with corrective feedback, 2) single-category exposure followed by testing without feedback, and 3) no prior exposure, testing with corrective feedback. Each trial, participants gave their best guess for object category and their confidence. All participants demonstrated category learning. Group (3) achieved the best performance, a level of 83% relative to the Bayesian observer. Intriguingly, performance did not asymptote, suggesting that further improvement with additional training is possible. Future studies will test this prediction in order to determine the extent to which human haptic performance can approach optimality.

1-D-142 *Characterization of motor and sensory deficits of a photothrombosis-induced perinatal stroke mouse model*

Sarah Zhang[1], Isabelle Sinclair-Takoff[1], Greg Silasi[1]

[1]University of Ottawa

Intro & Objectives: Perinatal stroke, which occurs before and closely after birth, can lead to significant motor and cognitive deficits. Using a mouse model of perinatal stroke we sought to investigate the relationship between motor function and cortical motor maps in adult mice. Methods: A photothrombotic stroke was induced in the primary motor cortex (M1) in P7 Thy1-ChR2 mice. Following a transcranial window implant, motor maps were created through optogenetic point stimulation of both hemispheres. Sensorimotor function was evaluated through a battery of fine and gross motor tests, including tapered beam, adhesive tape test, Schallert's cylinder, and the single pellet reaching task. Results: Focal M1 stroke injury in neonatal pups decreased the cortical representation of the impaired forelimb by 78% in the contralateral and 68% in the ipsilateral hemisphere. Additionally, preliminary results show P7 stroke decreasing contralesional paw preference during cylinder test and decreasing sensorimotor integration in the adhesive tape test. Conclusions: Motor representation and output is impaired in the injured hemisphere compared to sham controls. These cortical changes manifest in long-term motor deficits which can be detected into adulthood.

1-D-143 *Electrophysiological characterization of hIPSC-derived sensory neurons using a small molecule inhibition protocol reveals a heterogeneous population of neurons*

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Lee Lesperance[1], Sazia Sharmin[1], Wei Wei[1], Alina Piekna[1], Deivid Rodrigues[1], James Ellis[1], Steve Prescott[1]

[1]The Hospital for Sick Children

Human induced pluripotent stem cells (hIPSCs) are proving to be valued tools in human disease characterization and represent the forefront of patient-specific medicine. Through modulation of specific developmental pathways using small molecule inhibitors, differentiations can be guided to produce an array of neuronal types. Using this approach (Chambers et al 2012), neurons can be generated at a faster pace compared with previous methods. One of the confines surrounding the use of hIPSC-derived neurons however is the variability in fully differentiated cultures. Here we report an electrophysiological assessment of hIPSC-derived primary sensory neurons (hIPSC-PSN). Our results highlight the heterogeneous physiological profiles of the cells, suggesting that while repetitive spiking nociceptors represent the majority of the population, other neuron types are present. While certain electrophysiological properties of these neurons such as resting membrane potential and action potential half-width are consistent with values from human cadaveric dorsal root ganglion (DRG) neurons, other properties such as rheobase and soma diameter differ suggesting deviations in ion channel expression and morphological development as compared to human DRGs. Future work will focus on validating these neurons as models for studying the underlying mechanisms of neuropathic pain and human disease using electrophysiology/imaging based approaches. These findings suggest that attention should be taken when interpreting the physiology of hIPSC-PSNs and the need for cell specific characterizations.

1-D-144 *Laminar organization of conflict monitoring and goal maintenance signals in the medial frontal cortex*

Amirsaman Sajad[1], Steven Errington[1], Jeffrey Schall[1]

[1]Vanderbilt University

The medial frontal cortex (mFC) plays an essential role in inhibition of impulsive and execution of appropriate behaviors. However, the underlying cortical microcircuitry is unknown. To address this, we sampled neurons across all layers of a cortical area in mFC, known as supplementary eye field. Neural discharges were recorded from two macaque monkeys while performing an eye movement stop-signal task. On most trials monkeys were rewarded for looking at a peripheral visual stimulus, but occasionally a stop-signal instructed them to inhibit the movement. In our sample of 575 units, none were modulated early enough to contribute to reactive stopping, but 160 modulated after successful stopping. Transient response facilitation was observed in 53 neurons in Layers 3 (L3), L5 and L6, which scaled with the probability of stopping, qualifying them as putative conflict-monitoring neurons. Prolonged facilitation was observed in 42 neurons (mainly

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narrow-spiking) with a majority in L2/3 and a minority in upper L6. Prolonged suppression was observed in 65 neurons (mainly broad-spiking) which were mainly in L3 and L5 but also in lower L6. We propose that these antagonistic prolonged responses comprise a circuit enacting goal (i.e., fixation) maintenance following successful stopping. Collectively, these results complement previous reports (e.g., Sajad et al. 2019 Nature Neuroscience), revealing the laminar microcircuitry of cognitive control signals. This work was supported by R01-MH55806, P30-EY08126, and the Ingram Chair in Neuroscience

E - Homeostatic and neuroendocrine systems

1-E-145 *Vasopressin Receptor 1a defines mechano and thermosensitive neurons in rat OVLT.*

Cristian Zaelzer-Perez[1], Charles Bourque[2]

[1]Research Institute of the McGill University Health Centre, [2]McGill University

The organum vasculosum lamina terminalis (OVLT) is a circumventricular organ that lies in front of the third ventricle where detects variations in systemic osmolality carried by the blood and cerebrospinal fluid (CSF). It contains the product of at least two different mRNAs derived from the TRPV1 gene, Trpv1 (TRPV1 WT) and Trpv1dn (ΔN-TRPV1). The proteins encoded confer different temperature and osmotic sensitivity properties to these neurons (Zaelzer et al. 2015). Recently, using a mix of electrophysiology, single cell RT-PCR, pharmacology, and temperature stimulation protocols we explored the distribution of the neurons containing those transcripts in an effort to find markers to study differentially the two populations. Our results show a molecularly well-defined population of neurons co-expressing Trpv1dn and the Vasopressin Receptor 1a transcript, Avpr1a; Patch Clamp analysis shows that these neurons respond to negative pressure, and showed significant reduction in the firing activity after SB366791 was added in the bath. Based on theses findings we engineered a virus with the promoter for Avpr1a driving the expression of TdTomato (TOM) and then injected into the OVLT and MnPO areas on rat brains. Fifty days post injection we recorded the responses to negative pressure, temperature, and the immunohistochemistry makeup of the cells positive for TOM signal. While a large proportion of TOM neurons display mechano- and thermos sensitivity, immunostaining will be used to verify specificity of AAV-mediated reporter expression and will be presented at the poster.

1-E-146 *Role of glutamate co-expression in melanin-concentrating hormone neurons in the lateral hypothalamus*

Aditi Sankhe[1], Dillon Bordeleau[1], Diana Alfonso[1], Gabor Wittmann[2], Melissa Chee[1]

[1]Carleton University, [2]Tufts Medical Center

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Melanin-concentrating hormone (MCH) is produced exclusively in the lateral hypothalamus and almost all MCH neurons co-express the vesicular glutamate transporter 2 (vGLUT2) and can release glutamate. MCH has known roles for regulating rapid eye movement (REM) sleep and promoting positive energy balance. The loss of MCH results in reduced body weight, increased energy expenditure, and dysregulated REM sleep. Glutamate synergizes with MCH to regulate REM sleep, but the role of glutamate in MCH-mediated feeding behaviours is still being established. To determine if glutamate plays a role in MCH-mediated feeding behaviours, we deleted vGLUT2 from MCH neurons by crossing a Mch-cre mouse with a Vglut2-flox mouse. The resulting Mch-Vglut2-KO mice showed at least 83% deletion of Vglut2 mRNA from MCH neurons. Loss of vGLUT2 did not alter food intake or baseline locomotor activity, thus Mch-Vglut2-KO mice have the same body composition and body weight as Vglut2-flox controls. We determined the response of Mch-Vglut2-KO mice to a high fat diet. Interestingly, while Mch-Vglut2-KO mice will typically consume 25.6% more of the palatable diet during the first day of exposure, Mch-KO mice do not. This indicates that the loss of glutamate release from MCH neurons had no effect on homeostatic feeding or weight gain but facilitates hedonic feeding. This suggests that the synergistic roles of glutamate and MCH to regulate REM sleep are not seen for energy balance. Rather, glutamate release from MCH neurons is context-dependent and may antagonize the effects of MCH-mediated feeding behaviour.

1-E-147 *Salt loading increases mechanosensitivity (osmosensitivity), and enhances cytoskeletal components within vasopressin neurons of the rat supraoptic nucleus*

Joshua Wyrosdic[1], David Levi[1], Masha Prager-Khoutorsky[1], Charles Bourque[2]

[1]Research Institute of the McGill University Health Centre, [2]McGill University

High dietary salt intake is a major risk factor for hypertension and is strongly correlated with the incidence of cardiovascular diseases and stroke. In this study, VP-eGFP Wistar rats were subjected at random to two treatment groups which ultimately induced hypertension. One by which was a salt-loading period where their drinking water was replaced with 2% NaCl (SL). The other, a dietary intervention (high salt chow) combined with an infusion of angiotensin II via an SubQ osmotic mini pump (AngII). Patched cells were exposed to a hyperosmotic stimulus in slices, or negative pressure in isolated cells. Current clamp analysis revealed that the excitatory response of VP MNCs to hypertonicity was enhanced following SL and AngII. However, the membrane depolarization induced by acute hypertonicity was greater in the SL group opposed to the euhydrated (EU) and AngII rats. Current clamp analysis of isolated VP MNCs showed that reducing cell volume caused greater depolarization of the membrane potential in SL vs EU & Ang II. Moreover, this effect was associated with a greater enhancement of action potential discharge frequency in SL. Lastly, the decrease cell volume prompted by negative pressure was significantly smaller in the SL group; suggesting cytoskeletal enhancement. Quantification of F-actin and

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tubulin using fluorescent staining show an increase in in the density of both cytoskeletal components in the SL group compared to the AngII and EU. These results suggest that SL causes an increase of mechanosensitivity, as well as cytoskeletal enhancement within VP MNCs.

1-E-148 *Induction of c-Fos in distinct brain regions following acute treatment with live, but not heat-killed bacteria through vagus nerve-dependent and independent pathways*

Aadil Bharwani[1], Christine West[2], Karen-Anne McVey Neufeld[2], John Bienenstock[2], Paul Forsythe[2]

[1]St. Joseph's Healthcare Hamilton, [2]McMaster University

While the literature is replete with evidence of gut-brain signalling, the brain regions that are recruited in response to bacterial signals are unknown. Additionally, although several pathways have been proposed to mediate such interactions, it is unclear whether bacteria recruit multiple pathways that transmit information to distinct regions. Male Balb/c mice were orally administered a single dose of saline or live or heat-killed Lactobacillus rhamnosus (JB-1). 165 minutes later, depression-like behaviour was measured during the tail suspension test, mesenteric vagal afferent fibre firing was recorded, and c-Fos immunoreactivity in the brain was mapped. In a second experiment, mice underwent a sub-diaphragmatic vagotomy or sham surgery to investigate whether severing the vagus abolished JB-1-induced c-Fos expression. Live, but not heat-killed bacteria significantly induced c-Fos expression in the basolateral and central amygdala, ventral hippocampus, periaqueductal grey, dorsal raphe nucleus, and locus coeruleus. Both live and heat-killed bacteria increased c-Fos expression in the paraventricular nucleus of the thalamus and facilitated firing of vagal fibres absent behavioural changes. Severing the vagus prevented JB-1-induced c-Fos immunoreactivity in all regions except the ventral hippocampus and dorsal raphe nucleus. These data identify regions that respond to bacteria-derived signals and indicate the recruitment of multiple signalling pathways. Future research will need to identify these signals and describe the effects of acute versus chronic signalling.

1-E-149 *Adipose Triglycerides Lipase (ATGL) in mediobasal hypothalamic neurons plays a key role in energy homeostasis regulation.*

Romane Manceau[1], Sebastien Audet[1], Arturo Machuca Parra[1], Khalil Bouyakdan[1], Alexandre Fisette[1], Demetra Rodaros[1], Grant Mitchell[2], Stephanie Fulton[1], Thierry Alquier[1]

[1]CRCHUM - Université de Montréal, [2]Ste Justine Hospital

Adipose Triglyceride Lipase (ATGL) acts as the first lipase in the hydrolysis of triglycerides (TG). Recent studies show that ATGL in peripheral tissues plays major roles on energy homeostasis.

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We found that ATGL is expressed in the mediobasal hypothalamus (MBH) and in hypothalamic neuronal cell lines, in line with our recent study suggesting that neurons accumulate TG. ATGL expression is increased in the MBH of fasted mice and in high fat fed mice that maintain a healthy body weight compared to mice that become obese. This suggests that increased ATGL may play a role in maintaining a healthy metabolic profile. We propose that hypothalamic ATGL regulates lipid metabolism in the brain that in turn contributes to energy balance. To test this hypothesis, synapsin-Cre or -GFP expressing AAV are stereotaxically injected in the arcuate nucleus of male ATGL flox mice to KO ATGL specifically in neurons (AKO). First, we validated that ATGL expression is reduced by 50% in AKO mice. We found that AKO have increased weight gain on a chow diet compared to control animals that is associated with reduced energy expenditure and increased food intake and fat mass. In addition, chow-fed AKO mice have an increased fasting glycaemia and mild glucose intolerance. Finally, pharmacological inhibition of ATGL in hypothalamic neurons in vitro increases intracellular TG content. Together, our findings suggest that the ATGL pathway in MBH neurons beneficially regulates glucose and energy homeostasis by mechanisms that may involve regulation of TG and lipid droplets metabolism.

1-E-150 *Disruption of circadian rhythms by shiftwork and effects on alcohol consumption*

Abanoub Aziz Rizk[1], Bryan Jenkins[1], Yasmine Al-Sabagh[1], Cristine Reitz[1], Mina Rasouli[1], Tami Martino[1], Jibran Khokhar[1]

[1]University of Guelph

INTRODUCTION: Circadian rhythms can be disrupted due to shiftwork, travel, and changes in seasons. These disruptions induce desynchrony between the environment and the internal circadian rhythm and have been linked to a higher likelihood of binge drinking. In addition, ClockΔ19 mouse models, with altered circadian rhythms, exhibit amplified sensitivity to rewarding substances, such as alcohol, compared to wild type (WT), suggesting that they may be at a greater risk for addiction. Our aim is to investigate the effects of environmental and genetic circadian rhythm disruptions on alcohol consumption in a gene-environment interaction study. METHODS: Twenty-four adult male WT and ClockΔ19 mice (twelve of each genotype) were housed in pairs. Each mouse was given ad libitum access to one bottle with 10% alcohol and one with water. Mice were either housed on a normal 12h:12h Light: Dark (LD) cycle or a 10h:10h LD (shiftwork model) cycle, with alcohol, water and house chow provided ad libitum. RESULTS: WT mice housed on the 10:10 LD cycle consumed more alcohol than mice housed on the 12:12 LD schedule during the first week, but this difference resolved throughout the study period. It appears therefore, that circadian rhythm disruptions in WT may lead to an acute increase in alcohol consumption. Future work will assess the effects of the ClockΔ19 mutation and altered diurnal cycles on alcohol

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consumption. The study is significant as both diurnal variations and genetic variations in diurnal genes are considered a risk factor for alcohol drinking resulting in negative health effects.

1-E-151 *Identifying molecular mechanisms of socially-mediated pubertal suppression*

Mariela Faykoo-Martinez[1], Dustin Sokolowski[1], Zaichao Zhang[1], Kyoko Yuki[2], Troy Collins[1], Mark Palmert[2], Michael Wilson[2], Melissa Holmes[3]

[1]University of Toronto, [2]The Hospital for Sick Children, [3]University of Toronto Mississauga

Pubertal timing is highly heritable yet influenced by environmental conditions including psychosocial stressors. Pubertal timing, its susceptibility to social modulation, and associated health outcomes, all differ between males and females. Thus, understanding sex-specific and sex-similar mechanisms controlling pubertal timing has tremendous importance for human health. The naked mole-rat (NMR) is a unique rodent residing in large colonies of adults who remain in a pre-pubertal state due to the presence of a single, dominant breeding pair. How puberty is suppressed in adult NMRs is unknown, though sex differences in mechanism likely exist (e.g., males show reduced suppression). To discover molecular mechanisms contributing to socially-mediated reproductive suppression we are comparing gene expression profiles in candidate tissues obtained from both sexes within the colony (breeders and subordinates) to animals that have been removed from their colony for 1 or 4 weeks, which triggers pubertal onset. Using RNA-seq, we are profiling six reproductively- and socially-relevant regions of the brain, pituitary and gonads. We have identified gene modules in the dorsal hypothalamus (stress inputs) and ventral hypothalamus (control of pubertal timing) that differ by social/reproductive status and sex. Overall, we find more changes in the female gene expression profile across the transition. For example, genes involved in dopaminergic pathways are lower in females removed from colony-living relative to other groups. Gene expression profiling in other regions is currently underway.

1-E-152 *Dinner for two: Digging into how ghrelin & endocannabinoid systems regulate feeding in the VTA*

Alexander Edwards[1], Lindsay Hyland[1], Matthew Hill[2], Melissa Chee[1], Alfonso Abizaid[1]

[1]Carleton University, [2]University of Calgary

Ghrelin and endocannabinoids (eCBs) stimulate food intake by activating growth hormone secretagogue receptors (GHSRs) and cannabinoid receptors (CB-1Rs), respectively. In the hypothalamus (HYP), which regulates hunger driven feeding, ghrelin and eCB systems depend on one another to promote food intake. GHSRs and CB-1Rs are also expressed in the ventral tegmental area (VTA), an integral brain region for reward and motivated behaviours. Stimulation

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of GHSRs or CB-1Rs within the VTA leads to the activation of dopaminergic (DA) neurons and consequently increases food motivation and consumption. However, the interdependence of ghrelin and eCB systems within the VTA remains unclear. To this end, we conducted experiments to test if ghrelin and eCB systems interact within the VTA and if their interaction is important for regulating feeding behaviours. We find that GHSR-deficient rats have reduced VTA eCB tone and transcription levels of important eCB system proteins relative to WTs. Second, we determined that peripheral and intra-VTA injections of a CB-1R antagonist attenuate the known ability of intra-VTA ghrelin to increase food intake and promote feeding motivation in progressive ratio studies. Interestingly, CB-1R antagonism did not block the ghrelin-mediated stimulation of VTA DA cells in our electrophysiological recordings; thus, the site of ghrelin and eCB interaction is not at DA cells in the VTA. Studies are underway to investigate if the interaction of these systems occur at presynaptic sites upstream of VTA DA neurons.

1-E-153 *Electrophysiological effects of neurotensin on subfornical organ neurons*

Colleen Peterson[1], Mark Fry[1]

[1]University of Manitoba

Neurotensin is a pleiotropic signaling molecule with metabolic and cardiovascular activities. The subfornical organ (SFO) has well-recognized roles in energy homeostasis, hydromineral balance, and cardiovascular output, and has at least two neurotensin inputs: circulating neurotensin in the blood, and neurotensinogenic projections from the arcuate nucleus of the hypothalamus. Moreover, a previously published SFO transcriptome shows high expression of neurotensin receptor transcripts NTSR2 and NTSR3, suggesting neurotensin plays a signalling role at the SFO. We sought to characterise the electrical properties of neurotensin signalling on SFO neurons. Current clamp recordings show that at a dose of 100 nM, neurotensin depolarises and increases the action potential frequency of 53% of SFO neurons. Furthermore, voltage clamp experiments revealed that neurotensin attenuates IA and IK potassium currents in 50% of SFO neurons, and increases sodium current amplitude in 25% of SFO neurons. The robust response and high receptor transcript expression levels suggest SFO is a key site of action for neurotensin. Future experiments will explore physiological effects of neurotensin at SFO and determine second messenger signaling pathways involved.

1-E-154 *An in vivo electrophysiology study of neurons in the paraventricular nucleus of the hypothalamus responding to stress*

Aoi Ichiyama[1], Kaela Scott[2], Brian Allman[2], Wataru Inoue[2]

[1]Western University, [2]University of Western Ontario

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A hallmark of the stress response, the activation of the hypothalamic-pituitary-adrenal (HPA) axis, starts with the release of corticotropin releasing hormone (CRH) from neuroendocrine neurons in the paraventricular nucleus of the hypothalamus (PVN). Although it is generally believed that CRH release is encoded by the firing activities of PVN-CRH neurons, the in vivo firing activity of these neurons remain unknown as traditional electrophysiology methods are unable to distinguish neurons intermingled in the PVN by their neurochemical identities. To investigate this, we used a combination of optogenetics and electrophysiology to "tag" the in vivo firing activity of CRH neurons by expressing light-activated channelrhodopsin (ChR2). In anesthetized, head-fixed mice, we recorded spontaneous single unit firing activities of PVN neurons during a no stress baseline and following stressful sensory stimuli (sciatic nerve stimulation). The spontaneous activity of PVN-CRH neurons were identified by light-induced, short latency activity of ChR2-expressing CRH neurons. We found that sciatic nerve stimulation increased the firing frequency of a subset of PVN neurons. Light stimulation of ChR2-expressing CRH neurons also independently increased firing frequency. Finally, we observed both light and sciatic nerve stimulation induced increased activity in the same recording. This is the first demonstration of firing activities of identified PVN-CRH neurons in vivo.

1-E-155 *Low dose gestational BPA exposure alters circadian rhythms in mice*

Dinu Nesan[1], Michael Antle[1], Deborah Kurrasch[1]

[1]University of Calgary

We have previously identified the hypothalamus as particularly susceptible to developmental disruption by Bisphenol A (BPA), a well-characterized endocrine disruptor that can act via multiple endocrine receptors. Low-dose gestational exposure causes accelerated hypothalamic neurogenesis and altered behavior, including hyperactivity, in zebrafish and mice. The suprachiasmatic nucleus (SCN) of the hypothalamus regulates the circadian clock, and we hypothesize a link between altered SCN function and hyperactivity in BPA-exposed animals. Here we present the effects of low-dose, environmentally relevant gestational BPA exposure on circadian rhythms in mice. We exposed mice to BPA (50 µg/kg-diet fed to pregnant dams) in utero, then recorded their activity during a 12:12 light/dark (l/d) cycle, then in 24h darkness (d/d). In l/d, BPA mice were more active than controls, exhibited longer activity duration, but displayed less anticipatory activity prior to the daily light/dark transition. Circadian disruptions in BPA mice were exacerbated by d/d conditions. BPA mice again showed significantly higher activity and longer activity duration, but without daily light cues, BPA-exposed mice had a significantly shorter circadian period. BPA mice also entrained more quickly to unexpected changes in photoperiod. Finally, we find these BPA-mediated alterations in activity and periodicity correlate with increased SCN vasopressin expression. We conclude that low-dose gestational BPA exposure disrupts the

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SCN and circadian clock, the first such finding in a mammalian model in vivo, and that this appears to be a contributing factor to hyperactivity in BPA-exposed mice.

F - Cognition and behavior

1-F-156 *Interaction between a polygenic risk score for fasting insulin and socioemotional development in children*

Aashita Batra[1], Zihan Wang[1], Irina Pokhvisneva[1], Michael Meaney[1], Patricia Silveira[1]

[1]McGill University

While the co-morbidity between metabolic and psychiatric disorders is well-established, the mechanisms are poorly understood, and exposure to early life adversity is a common developmental risk factor. There is high co-occurrence of several psychiatric diseases with insulin resistance. Our hypothesis is that the genetic profile associated with higher fasting insulin interacts with postnatal adversity, influencing anxiety and related outcomes (Dominique task) in children. We calculated a PRS for fasting insulin in children from the MAVAN cohort (Scott et al 2012) and estimated their adversity exposure using a cumulative score involving different environmental variables. Interactions between fasting insulin PRS (p threshold p=0.001) and adversity exposure were significant for general anxiety and phobia according to the differential susceptibility framework, in which the high ePRS group had higher or lower anxiety (β=0.9233, p=0.005) and more or less phobia (β=0.4214, p<0.005) according to the exposure to higher or lower environmental adversity respectively. Differential susceptibility states that individuals may vary both by exhibiting poor responses when exposed to adverse environments, and disproportionally benefiting from positive settings. Enrichment analysis on Metacore shows the genes included in the PRS are enriched for regulation of insulin secretion as expected (p<0.001). A fasting insulin polygenic score can moderate the impact of different environmental exposures on the onset of anxiety and phobia.

1-F-157 *The key for brain exercises to be effective for cognitive function is its delivery mode*

Zahra Moussavi[1], Cassandra Aldaba[1], Sogol Masoumzadeh[1], Duy Tran[1], Maria Uehara[1], Brian Lithgow[1]

[1]University of Manitoba

We developed 7 games within a Brain Fitness App based on the premise of brain plasticity to improve spatial orientation and associative memory that are known to decline with normal aging

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and dementia. 23 cognitively healthy individuals (69.8±5.9 yr) and 12 with mild cognitive impairment (MCI) or early stage Alzheimer's (68.9±8.2 yr) were enrolled. Cognitively healthy participants used the App at home at their own pace but were advised to use it daily. Seven of the MCI/Alzheimer's group used the App with a tutor at our center 5 day/week for 4 consecutive weeks, two blocks of 30 minutes per day with 40 min break between the blocks. The cognitive function of both groups was assessed by WMS at baseline and immediately post-intervention. We investigated the practice effect of the WMS in a number of participants in each group with two baseline assessments one month apart before using the App. When accounting for the practice effect of the WMS test, the observed improvement in healthy group post-intervention was not significant. This could also be due to ceiling effect of the assessment as the majority of this group had a high score of WMS at baseline. Also, our logged data indicate the majority did not use the games as frequently as instructed. There was no WMS practice effect in MCI/Alzheimer's group, and those who were tutored showed a significant improvement post-intervention. Our results indicate, especially for MCI and Alzheimer's individuals, having a tutor in a regimented learning environment is the key for these brain exercises to be effective in improving cognition.

1-F-158 *Atomoxetine prevents working memory loss in hyperactive rats, mediating plastic changes in prefrontal cortex pyramidal neurons*

Néstor Martínez-Torres[1], David González-Tapia[2], Myrna Nallely Vázquez-Hernández[2], Ignacio González-Burgos[2]

[1]Universidad de Guadalajara/ Instituto Mexicano Del Seguro Social, [2]Instituto Mexicano Del Seguro Social

Attention Deficit Hyperactivity Disorder (ADHD) causes impaired visuospatial working memory (VWM), which primarily maps to the prefrontal cortex. However, little is known about the synaptic processes underlying cognitive loss in ADHD, or those ultimately involved in the preventive effect observed through the clinical use of Atomoxetine (ATX). To investigate the plasticity underlying ADHD related cognitive loss, and that potentially involved in the preventive action of Atomoxetine, allocentric VWM was assessed, as well as the dendritic spine number and proportional density on pyramidal neurons in the prefrontal cerebral cortex layer III of neonatal 6- hydroxydopamine-lesioned rats. The effect of acute ATX treatment was also assessed at 28 days of age. 6-OHDA induced lesions produced increased motor activity and a loss of VWM, concomitant with a reduction in thin spine density. ATX administration reversed cognitive loss, in conjunction with a decrease in thin spines and an increase in mushroom spines. A reduction in the proportion of spines involved in learning in hyperactive animals could account for the loss in cognitive function observed. Considering thin spine density was also reduced after ATX administration, we hypothesized that the restoration in cognitive function recorded could be brought about by an increase in memory related mushroom spines.

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1-F-159 *Hierarchical architecture of the human brain during external and internal attention*

Julia Kam[1], Jack Lin[2], Anne-Kristin Solbakk[3], Tor Endestad[3], Pål Larsson[4], Robert Knight[1]

[1]University of California, Berkeley, [2]University of California, Irvine, [3]University of Oslo, [4]Oslo University Hospital

Prevailing theories of top-down control converge on the role of the frontal cortex in facilitating selective attention to behaviorally relevant external inputs. However, the neural architecture supporting sustained attention directed to either the external or internal environment is less well understood. To address this, we used intracranial EEG to characterize the spatiotemporal dynamics of external and internal attention during a modified version of auditory target detection task. Participants directed their attention externally to auditory tones and responded to infrequent target tones, or internally to their own thoughts while ignoring the tones. We compared high frequency band activity (HFA; 70-150Hz) in response to target and standard tones across the lateral and temporal cortices during external and internal attention. The target detection response, as indexed by increased HFA to target tones relative to standard tones, was larger and peaked later in the frontal relative to temporal cortex across both attention states. Importantly, only the frontal HFA response was larger during external relative to internal attention. Taken together, these results provide evidence that the frontal cortex plays an important role in the top down control of attention to both the external and internal environments.

1-F-160 *Polygenic differential susceptibility to adversity and ADHD problems in children: the expression based Insulin-receptor Polygenic Score*

Bruna Regis Razzolini[1], Zihan Wang[1], Irina Pokhvisneva[1], Michael Meaney[1], Patricia Silveira[1]

[1]McGill University

Dopaminergic neurons are involved in the individual's response to environmental conditions. Insulin acts on mesocorticolimbic areas regulating changes in dopamine (DA) neurotransmission and hence can affect DA-related behaviours. Using a biologically-informed polygenic score based on genes co-expressed with the insulin receptor (ePRS-IR) in the mesocorticolimbic system, we investigated its interaction with the early life adversity on ADHD problems (Childhood Behavior Checklist, CBCL) in a cohort of children at 48 and 60 months (MAVAN). A list of genes co-expressed with the insulin receptor gene was created, and the effect size of the association between each individual SNP from these genes (post-clumping) and gene expression data (GTEx) provides the biologically-informed polygenic score (ePRS-IR). Postnatal adversity was evaluated through many variables aggregated in a cumulative score "A" (e.g. hospitalizations, maternal

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depression, low SES). There is an interaction between the ePRS-IR and the A-Score on ADHD Problems score at 48 months (β= -0.81 ;p<0.001) and 60 months of age (β= -0.75 ;p<0.001). Evidence for the differential susceptibility hypothesis according to Roisman et al (2012) was found in both cases, in which the high ePRS-IR groups has more problems as adversity increases, but less problems in supportive environments. This emphasizes the importance of prevention and how a positive postnatal environment has a positive impactonn children's health.

1-F-161 *Developing a translational polygenetic risk score of differential susceptibility*

Maeson Latsko[1], Zihan Wang[1], Tie Yuan Zhang[1], Michael Meaney[1], Patricia Pelufo Silveira[1]

[1]McGill University

The differential susceptibility hypothesis postulates that malleable or "plastic" individuals are hyper-responsive to the environment; supportive environments will promote positive behavioral outcomes, while adverse environments will result in behavioral problems. To empirically test whether malleable individuals share common transcriptional patterns of gene expression, we calculated a polygenic risk score (PRS) for environmentally responsive genes in mice (C57BL6/J). RNA sequencing of ventral dentate gyrus tissue revealed common patterns of genes transcription in mice exposed to environmental enrichment (P21-P77) or mice that displayed social avoidance behavior in response to adult chronic social defeat. This PRS score was weighted using the GWAS for Major Depressive Disorder (MDD) and tested on children within the MAVAN cohort. Results revealed a significant interaction between the PRS score and CBCL Anxiety problems ($\beta = -809.6$, $p < 0.001$), such that individuals with high PRS based on environmentally responsive genes were less likely to develop anxiety in supportive contexts, or more likely to develop anxiety in adverse contexts ($p < 0.001$). Importantly, this pattern did not persist in individuals with low PRS of the same gene network ($p > 0.05$). These data confirm that individuals who display behavioral plasticity share common gene networks that lead to susceptibility or resilience in respond to the environment.

1-F-162 *The effect of stress-relieving visual cues in health communication and its neurobiological and psychological pathways*

Zhenfeng Ma[1], Andre Portella[2], Laurette Dube[2]

[1]Wilfrid Laurier University, [2]McGill University

Here we examine the effect of stress-relieving visual cues on consumers' acceptance of health communication by inducing health-related stress using mental imagery tasks and exploring critical neurobiological pathways underlying its impact. We also explored the possibility that the signaling

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value of neurobiological pathways may be modulated by the stress-relieving positive cues. We propose that perception of a health threat activates autonomic, endocrine, as well as affective response to the stressor and that positive visual cues in health communication enhances consumers' acceptance of the communication by turning the lingering physiological responses from an otherwise negative impact into a positive effect on persuasion. Seventy-four healthy women (Mage = 58, SD = 7.0) from the local community were tested in a 2x2 experimental study (stressful vs. non-stressful) × (presence vs. absence of stress-relieving cues) between-subject design. We found that mental imageries about a stressful (vs. non-stressful) health scenarios increased reactivity in the autonomic and endocrine stress markers (i.e., heart rate variability and salivary cortisol). Among consumers who had encountered a perceived health threat, positive visual cues resulted in a more favorable attitude toward the communication. Furthermore, positive peripheral cues reversed the otherwise negative impact of cortisol and HRV and turned these responses into positive effects on persuasion. Such persuasive pathways, however, was not evident for self-reported affect and risk perception.

1-F-163 *Red preferentially strengthens response inhibition in a stop signal paradigm where color change occurs at a spatially separated location*

Gifty Asare[1], Saloni Phadke[1], Heather Jordan[1], Mazyar Fallah[1]

[1]York University

Color impacts many fields including user interfaces, sporting events, and driving. More recently, we have shown that an intrinsic color hierarchy affects visual processing by modulating response inhibition such that, response inhibition but not execution was affected differently by red and green colored stimuli. To further study the role of color in cognitive processes, our first aim was to identify whether this effect was due to color opponency, color space, or specific to red/green by testing red, green, yellow and blue. Our second aim was to determine if color modulation of response inhibition was contingent upon the color change occurring on the target. In the present study, we used a modified stop signal paradigm where the stop signal was a task relevant color change appearing on a box placed above or below the target. In the first experiment, participants performed the SST with red and green colors and we observed that stop signal reaction times were faster for red than green, replicating our prior result. In the second experiment, participants were tested with yellow and blue stop signals and no difference was observed in stop signal reaction times. In a third experiment, we compared all four colors within subjects. Green stop signals were the slowest followed by blue, yellow, and then red. Post-hoc testing showed that red stop signals were significantly faster than green ones supporting that red facilitates and green delays response inhibition. These results suggest that color modulation of response inhibition is dependent upon the red/green color opponency.

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1-F-164 *Association of semantic priming deficits with role functioning in persons at clinical high risk for schizophrenia: Evidence from event-related brain potentials*

Jennifer Lepock[1], Romina Mizrahi[1], Margaret Maheandiran[1], Sarah Ahmed[1], Michelle Korostil[2], R. Michael Bagby[2], Michael Kiang[1]

[1]Centre for Addiction and Mental Health, [2]University of Toronto

Persons exhibiting clinical high-risk (CHR) symptoms similar to but less severe than those of schizophrenia have an elevated risk of developing this disorder. We previously found that CHR patients have reductions in the N400 event-related brain potential (ERP) semantic priming effect, indicating deficits in using meaningful stimuli to activate related concepts in semantic memory. We sought evidence that this abnormality is associated with real-world functional impairment in CHR patients, hypothesizing that N400 semantic priming deficits would correlate with lower social and role functioning in this group. Methods: We recorded continuous EEGs in 36 help-seeking CHR patients and 25 healthy control participants while they viewed 80 strongly related and 80 unrelated prime-target word pairs, and 160 word-nonword pairs, in a fixed randomized order, with stimulus-onset asynchrony (SOA) of 300 ms or 750 ms. Functional status was measured with the Global Functioning: Social and Role Scales. Results: There was a significant reduction in the N400 priming effect at the 750-ms SOA in CHR patients compared to controls (p=0.049). In the patients, smaller N400 priming effects at the 300-ms (but not the 750-ms) SOA correlated with lower role functioning (Spearman's = -0.37, p=0.03). Conclusions: The results suggest that although CHR patients in general are deficient in maintaining activation of related concepts over longer intervals after meaningful stimuli, a subset of patients with deficits in activating related concepts even at shorter intervals may be the most functionally impaired.

1-F-165 *Lateral habenula output pathways in depression*

Jose Cesar Hernandez Silva[1], Nikola Pausic[2], Christophe Proulx[1]

[1]CERVO Brain Research Centre, [2]CERVO brain research center

The Lateral habenula (LHb), the main disappointment center of the brain, is hyperactive in depression. However, how its neural outputs contribute to depression remains unclear. Here, we use optogenetics to characterize synaptic transmission from the LHb to two of its main output targets, the serotoninergic dorsal raphe nucleus (DRN) and the rostromedial tegmental nucleus (RMTg), in normal and depressed mice. An AAV encoding channelrhodopsine-2 fused to the fluorescent protein mCherry (AAV-ChR2-mCherry) was first injected in the LHb. Two weeks later, mice were subjected to 10 days of Chronic Social Defeat Stress, and 24h after, tested in the social interaction test. Acute brain slices were prepared from control and defeated mice, and synaptic transmission was measured using whole-cell patch clamp recordings. Voltage-clamp recordings from DRN neurons showed that optically-evoked AMPA/NMDA ratio is increased in susceptible

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mice compared to control and resilient mice. We observed no difference in the optically evoked paired pulse ratio (PPR) between groups. These results suggest postsynaptic potentiation at the LHb-DRN pathway in susceptible mice. In contrast, recordings from RMTg neurons revealed an increase in optically evoked presynaptic transmission (increased PPR) in both susceptible and resilient mice when compared to control mice, while no differences were observed in AMPA/NMDA ratio.These results suggest that LHb-DRN and LHb-RMTg may play distinct roles in behavioral and cognitive deficits found in depression.

1-F-166 *Prenatal noise stress aggravates cognitive decline and the onset and progression of β-amyloid pathology in a mouse model of Alzheimer's disease*

Zahra Jafari[1], Megan Ocuma[1], Hadil Karem[1], Jogender Mehla[1], Bryan Kolb[1], Majid Mohajerani[1]

[1]Lethbridge University

Environmental distresses occurring during the sensitive periods of early-life may exacerbate the vulnerability to develop physical and mental diseases in old age. Studies have shown the impact of prenatal stress (PS) on the endocrine development and reprogramming of hypothalamic-pituitary-adrenal (HPA) axis functions in association with cognitive development and susceptibility to neuropsychiatric diseases. Long-term exposure to glucocorticoids can damage the brain and intensify the progression of Alzheimer's disease (AD)-like neuropathological changes, especially in females. There is, however, less information as to the link between PS and the risk of developing AD pathology throughout the lifespan. In the present study, male and female APPNL-G-F/NL-G-F offspring of dams exposed to gestational noise stress were compared with the control offspring in corticosterone alternations, cognitive and motor performances, and the onset age and development of amyloid beta (Aβ) plaques across age. The hyperactivity of the HPA axis, spatial learning, and Aβ development were sex-specific showing persistent high levels of stress and further memory loss in females than males, especially in PS mice. The Aβ deposition was started earlier, by 2-3 months, and exhibited a heightened progression in PS animals. The PS also created a long-lasting anxiety-like behavior and impairment in cognitive function and motor coordination. Our results suggested PS as a risk to exacerbate AD-like neuropathological changes during the lifespan, with higher susceptibility of females. The findings were discussed in

1-F-167 *Lactate dehydrogenase expression in Drosophila melanogaster impacts lifespan and long-term courtship memory*

Ariel Frame[1], Anne Simon[1], Robert Cumming[2]

[1]Western University, [2]University of Western Ontario

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The brain is one of the most energetically expensive organs in the body. How brain cells maintain the energy to sustain their function likely varies with age, region of the brain and cell type. Metabolic coupling of neurons and glia has been shown in invertebrates such as honey bees and fruit flies (Drosophila melanogaster) as well as vertebrates such as rats, mice and chicken. Lactate is a key metabolite in neuronal function. Glycolytic metabolism of carbohydrates results in lactate production catalyzed by the enzyme lactate dehydrogenase (LDH). Alternatively, lactate can fuel oxidative metabolism, whereby lactate is converted back into pyruvate by LDH. Therefore, neurons may maintain energy production by glycolytically generating lactate or use lactate provided by glial cells to maintain energy production oxidatively. The latter, referred to as neuron-glia lactate shuttling, has been implicated in long-term memory (LTM) formation in vertebrates, but unstudied in the context of aging. Brain lactate metabolism's role in Drosophila memory has never been investigated. In this study we genetically alter Drosophila LDH (dLdh) expression in neurons and glia to test the impact on LTM at various ages. The courtship conditioning assay was used to test 24hr LTM. Endogenous dLdh was found to increase with age. Moreover, ectopic expression of dLdh in neurons or glia reduced lifespan. Preliminary findings show increased LTM in flies with decreased neuronal dLdh. These results suggest that elevated widespread brain lactate may actually be detrimental to the invertebrate brain.

1-F-168 *Effects of prenatal stress and/or forebrain atrx deficiency in C57BL/6 male mice on maternal care and emotional, cognitive and social development*

Gloria Rodrigues[1], Kristen Lee[1], Hillary Maillet[1], Donna Goguen[1], Ian Weaver[1]

[1]Dalhousie University

Early childhood experience and degree of parental-infant attachment influence brain development, notably in brain areas that support stress regulation, cognition and social behaviour. Animal models of gestational stress suggest that stable changes in gene expression (e.g. Atrx) in response to prenatal stress and/or natural variations in mother-pup interactions during the first week of postnatal life is mediated by changes in chromatin structure and DNA methylation. We compared the affiliative behaviour of mothers toward Atrx heterozygous (Atrx+/-) and wild-type (Atrx+/+) offspring during the first week of life as a function of prenatal experience (gestational restraint stress verses no restraint stress). Mothers provided less active maternal care and spent less time in contact with Atrx+/- offspring by comparison to Atrx+/+ offspring-- similar to gestational-stressed mothers. Stress during pregnancy and maternal behaviour influenced Atrx expression, and Atrx genotype influenced maternal behaviour toward the whole litter. As adults, offspring prenatally stressed and/or reared with Atrx+/- males showed altered Atrx gene regulation, reduced forebrain growth and increased anxiety, social avoidance and cognitive deficits--including Atrx+/+ female mice. Our findings demonstrate an unexpected role for ATRX in prenatal and early postnatal mouse development involving experiences of social and affiliative

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interactions, such as parenting, with a persistent effect on DNA methylation, hippocampus development, cognition, and anxiety-related and social behaviour in the adult offspring.

1-F-169 *Deep learning with segregated dendrites and multiplexing*

Jordan Guerguiev[1], Thomas Mesnard[2], Richard Naud[3], Blake Richards[4]

[1]University of Toronto Scarborough, [2]École Normale Supérieure, [3]University of Ottawa, [4]University of Toronto

In machine learning, deep learning (training many-layer neural networks) has led to human-level performance in complex learning tasks. The most common algorithm for deep learning, backprop, leads to emergent feature representations resembling those seen in the cortex. However, backprop is not biologically realistic for several reasons, including the need to switch between networks states for feedforward and feedback processing. It is unclear how the brain may implement something like backprop in order to achieve powerful learning in the cortex. Here, we demonstrate a biologically plausible form of deep learning at the level of neuronal ensembles, which combines the unique morphology of cortical pyramidal neurons and the theory of burst ensemble multiplexing developed by Naud & Sprekeler (2018). We use computational units representing ensembles of cortical pyramidal neurons, with somata receiving feedforward input and dendrites receiving feedback input. Feedforward weights in the network are trained in a way that approximates backprop using only information that is locally accessible to each ensemble. Importantly, the network does not need to switch between feedforward and feedback states in order to learn. Using this model, we can match the performance of backprop on standard visual recognition tasks, and generate experimental predictions about how neuronal ensembles may encode feedforward and feedback information. If evidence for this learning framework is found in the brain, it would be an important step in advancing our understanding of cortical learning.

1-F-170 *Changes in resting state neuronal networks and non-verbal learning in children with previous infantile hydrocephalus*

Ikhlas Hashi[1], Estelle Ansermet[1], Roy Eagleson[2], Sandrine de Ribaupierre[1]

[1]University of Western Ontario, [2]Western University

Infantile hydrocephalus (IH) is a neurological condition in which the normal flow of cerebrospinal fluid (CSF) of the ventricular system is obstructed. Ventricular dilatation can compress surrounding brain regions, with posterior brain regions such as the parietal cortex (PC) undergoing the worst extent of damage. Moreover, ventricle dilatation may have adverse effects on the development of resting state neuronal networks. We hypothesize that ventricular dilatation

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associated with infantile hydrocephalus will lead to decrease in overall global connectivity, particularly in posterior brain regions; as well decreased in non-verbal learning ability. A sample size of n = 13 aged 4-13 years was recruited, with 10 healthy controls and 3 children with previous IH. Participants underwent behavioural batteries: Beery Developmental Test of Visual-Motor Integration (Beery VMI), Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and Wechsler Intelligence Scale for Children (WISC); as well as resting state functional MRI (rsfMRI). IH patients were found to have significantly lower mean scaled score than the controls in non-verbal subtests of the behavioural assessments. Furthermore, the IH group also found to have significant changes in functional connectivity when compared to healthy controls, with the control group displaying stronger positive correlations than the patient group, with the greatest differences found in the PC.

1-F-171 *CRIPSR/CAS9 mouse model to study glutamate co-transmission by serotonin neurons of the dorsal raphe nucleus*

Lydia Saïdi[1], Christophe Proulx[2], Martin Parent[3]

[1]CERVO Brain Research Center, [2]CERVO Brain Research Centre, [3]Université Laval

Ascending serotonin (5-HT) projections arise mainly from the dorsal raphe nucleus (DRN). The vast majority of 5-HT DRN neurons express the atypical type III vesicular glutamate transporter (VGluT3), allowing co-release of glutamate and 5-HT by their axons terminals. The aim of this study is to generate and characterize a new mouse model to determine the role of glutamate co-transmission by 5-HT neurons of the DRN. To do so, we used CRISPR/Cas9 technology, allowing region and neuron-specific conditional knock-out, in adult mice. To knock-out the expression of VGluT3 specifically in 5-HT neurons of the DRN, an AAV encoding a guide RNA for the vglut3 gene was injected in the DRN of transgenic ePet-cre+/Cas9flox+ mice. RT-qPCR assay and immunohistochemistry confirm the depletion of VGluT3 in AAV-infected 5-HT neurons. Moreover, high-resolution confocal analysis reveals a decrease in the number of axon varicosities in VGluT3-depleted 5-HT neurons. In open-field behavioral test, VGlut3-depleted mice tend to show an increase in spontaneous motor activity as well as to remain at the periphery rather than the center of the arena. The shredding nestlet test also supports a high level of anxiety in our model. Moreover, VGluT3-depleted mice have a lack of interest for sweetened liquid reward. Using this model, we were able to highlight the involvement of VGluT3 in the regulation of anxious and spontaneous motor behaviors as well as in behaviors involving the reward system. In addition, our preliminary results suggest the involvement of VGluT3 in the maintenance of 5-HT axon morphology.

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1-F-172 *Development of neurocognitive remediation package for patients with schizophrenia in India: a pilot study*

Garima Joshi[1], Pratap Sharan[1], Kameshwar Prasad[1], Nand Kumar[1], V. Sreenivas[1], Ashima Nehra[1]

[1]All India Institute of Medical Sciences

Cognitive impairments tend to precede adaptive functioning impairment and have been related to functional outcomes. Effectiveness of treatment on functional outcomes is often overlooked in schizophrenia management in India. Being a problem of public health importance in India, it is important to explore new intervention strategies to help address cognitive dysfunction and create outreach for schizophrenia patients. Keeping in view the limitation of use of western rehabilitation packages on Indian patients, the objective of the study was to develop a neurocognitive remediation package for Schizophrenia patients which is culturally appropriate and free of education-bias targeting attention, memory, and executive functions. Remediation paradigms were developed to retrain the cognitive domains using the principles of repeated, massed practice and errorless learning and feedback in the current cognitive retraining paradigm. The package was standardised on 50 healthy controls to establish the feasibility of the paradigms, and to further carry out a pilot study using a Randomised Controlled Trial. The current abstract aims to present the methodology of development and standardisation of domain-specific, picture based, culture specific tasks to retrain affected cognitive abilities in patients with schizophrenia. The Developed Cognitive Remediation package has provided a base for an acceptable rehabilitation paradigm and will be further tested for effectiveness in a randomised controlled trial on schizophrenia patients in India.

1-F-173 *Effects of early-life maternal care received and dopamine receptor-2 genotype on brain dopamine levels and maternal behaviour in female rat offspring*

Hannan Malik[1], Samantha Lauby[1], Diptendu Chatterjee[2], Pauline Pan[1], Alison Fleming[3], Patrick McGowan[4]

[1]University of Toronto Scarborough, [2]SickKids Research Institute, [3]University of Toronto Mississauga, [4]University of Toronto

Variation in maternal licking/grooming of rat pups between and within litters has been demonstrated to influence offspring behaviour and gene expression, including propagation of maternal care across generations. Differential licking received by offspring and provided in adulthood to their offspring also affects dopamine levels within the nucleus accumbens (NAC) in both mother (F0) and adult offspring (F1). However, we do not know the extent the genetic background of the F1 offspring can influence this relationship. We explored a) whether gene x environment interactions are involved in regulating mesolimbic dopamine (DA) levels in the F1

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female offspring who had experienced within-litter differential levels of licking as pups and b) if this influences their own maternal behaviour. In the F1 offspring, we observed a significant positive correlation between DA levels within the NAC shell and maternal licking provided to their offspring. We also found for adult F1 offspring a sibling rank x Dopamine receptor-2 genotype (SNP RS107017253) interaction in DA levels in the NAC shell, where the high-licked siblings with the A/G genotype (as opposed to A/A) had the highest levels of extracellular DA. Lastly, we found that the level of DA in the NAC shell mediates the relationship between maternal licking received and their own maternal licking in females of the A/G genotype. Our findings suggest that genotype plays a role in the propagation of maternal licking provided across generations by changes in the dopamine levels of the maternal rat brain.

1-F-174 *Structural covariance networks among normal, high risk, and cognitively impaired older individuals*

Neda Rashidi-Ranjbar[1], Sanjeev Kumar[2], Benoit Mulsant[2], Nathan Herrmann[3], Linda Mah[4], Alastair Flint[5], Corrine Fischer[6], Bruce Pollock[2], Tarek Rajji[2], Aristotle Voineskos[2], on behalf of the PACt-MD Study Group[2]

[1]University of Toronto, [2]Centre for Addiction and Mental Health, [3]Sunnybrook Health Sciences Centre, [4]Baycrest Health Sciences, Rotman Research Institute, [5]University Health Network, [6]St. Michael's Hospital

Older individuals with a remitted major depressive disorder (rMDD) or mild cognitive impairment (MCI) are at a high risk of developing Alzheimer's disease (AD). However, it is unclear whether these groups demonstrate similar spatial distribution of cortical gray matter loss. The aim of this study was to investigate gray matter structural brain networks among rMDD, MCI, rMDD+MCI, AD, and healthy controls (HC). T1-weighted imaging scans were acquired in five groups: rMDD (n=43); rMDD+MCI (n=43); MCI (n=122); AD (n =39); and HC (n=35) age 60 and older. Graph theory analysis of 34 bilateral cortical thickness regions was conducted using: the minimum network density method, and a range of densities. Several network metrics were quantified and compared between each group pair with repetitions nonparametric permutation testing The HC group showed more frontal hubs and a distinct integration and segregation characteristics, representing near normal brain network. The AD group had higher modularity, lower global efficiency, and fewer hub nodes vs. other groups. The rMDD, MCI, and rMDD+MCI groups were largely undifferentiated on the clustering coefficient metric, however, the rMDD group had lower modularity compared to the other group. This may be due to treatment-responsive/resilience factor. The higher modularity of cortical organization in AD, rMDD+MCI, and MCI groups supports the disconnection hypothesis in neurodegenerative disorders. Subtyping participants with rMDD,

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MCI, or both to address their clinical heterogeneity might uncover additional differences in brain circuitry.

1-F-175 *Evaluation of the nomophobia's prevalence and its impact on school performance among adolescents in Morocco*

Ismail Louragli[1], Ahmed Ahami[1], Abderrazak Khadmaoui[1]

[1]University Ibn Tofail, Kenitra, Morocco

Social networks are a new form of addiction to technology and are beginning to take place in the moroccan society in the last decades, especially among children and adolescents. Furthermore the Nomophobia is a new form of addiction to new generations of mobile phones. Because of the importance of their speed spread and their influence on the person's future and interpersonal relationships, we conducted a study to calculate the degree of Nomophobia in adolescent population. It is through the establishment of a questionnaire for a sample of 541 adolescents including 298 girls and 243 boys of young Moroccans and a test on Nomophobia NMP-Q. The statistical result stated that 69.1% of girls and 63% of boys have Nomophobia in a moderate and severe state, and that the Smartphone is more solicited than the laptop with a negative correlation between school performance and the score of Nomophobia. Thus, poor school performance and mental disorders in adolescents can be explained by taking Nomophobia. Keywords: nomophobia, addiction, adolescents relationships, smartphone, social media, NMP-Q

1-F-176 *Uncovering the physical properties of clitoral stimulation: exploring paint bristle stiffness and conditioned partner avoidance in the female rat*

Marjolaine Rivest-Beauregard[1], Christine Gerson[1], Conall Mac Cionnaith[1], Eamonn Gomez-Perales[1], Uri Shalev[1], James Pfaus[2]

[1]Concordia University, [2]Universidad Veracruzana

Partner preference can be conditioned in the female rat using distributed clitoral stimulation (CLS) paired with a neutral odor cue yet little is known whether this technique can also be utilized to condition a partner aversion. We explored the feasibility of conditioned partner aversion by changing the bristle softness or stiffness - we define as tactile intensity - of the paintbrush utilized for CLS application. To assess the effect of CLS intensity on partner preference and/or aversion, forty-eight Long Evan female rats were ovariectomized (OVX) and hormonally primed with estradiol benzoate and progesterone. All females were randomly assigned to one of the four conditioning groups (n = 12/group): pure aversion (rough bristle odor vs. sham CLS no odor); rough bristle discrimination (rough bristle odor vs. soft bristle no odor); rough bristle non-

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discriminative (rough bristle no odor vs. sham CLS odor); and distributed discriminative (rough bristle no odor vs. soft bristle odor). All females underwent 12 conditioning trials prior to a final open field partner preference test, in which a scented and unscented male were tethered to opposite sides of the apparatus. Preliminary assessments (pure aversion, n = 6; rough bristle discrimination, n = 2; rough bristle non-discriminative, n = 2; distributed discriminative, n = 6) of the male from which the first ejaculation was received revealed no statistically significant differences within groups ($p > .05$). Therefore, bristle stiffness does not influence ejaculatory preference.

1-F-177 *Response in the avian hippocampal formation to incremental changes in context*

Chelsey Damphousse[1], Noam Miller[1], Diano Marrone[1]

[1]Wilfrid Laurier University

Response in the Avian Hippocampal Formation to Incremental Changes in Context Chelsey Damphousse, Noam Miller, Diano Marrone Department of Psychology, Wilfrid Laurier University, Waterloo, ON, N2L 3C5 Multiple avian species exhibit behaviours consistent with having cognitive maps. Recent data also show that many birds exhibit "place cell-like" patterns of neuronal activity. In mammals, we know that many different types of information can shift place cell mediated representations but information regarding what kinds of cues most powerfully drive spatial representation in the avian hippocampal formation (HF) is lacking. In the current experiment, quail were placed into an arena in which multiple cues were manipulated over two separate epochs (geometric properties of the arena itself, the objects within the arena, or both). Analysis via catFISH techniques allowed us to determine which condition caused the greatest proportion of remapping within the avian HF. These findings contribute to the potential discovery of an avian hierarchy of spatial information processing in which certain cues within the environment may be more salient and utilized more heavily during encoding of spatial environments.

1-F-178 *The effects of telencephalon lesions on zebrafish social behaviour*

Hailey Katzman[1], Noam Miller[1]

[1]Wilfrid Laurier University

Zebrafish are social animals that greatly benefit from observing and learning from the decisions they observe conspecifics making. Zebrafish form schools in which they are often closely packed together and polarized. While there are many models, and lab and field studies, of this behaviour, little is known about the mechanisms that influence these social interactions. The dorsal lateral

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telencephalon in zebrafish is thought to be analogous to the hippocampus in the mammalian brain, and fish are unable to solve spatial and contextual tasks when it is lesioned. As the hippocampus is used to encode social space and social memory in mammals, the analogous structure in zebrafish might be involved in schooling decisions. We performed excitotoxic brain lesions in the zebrafish telencephalon and allowed a single lesioned fish to school with four control fish in a small round tank, allowing us to examine changes in nearest neighbour distance, inter-individual distances, and the polarization of the group. We predicted that lesioned fish would have difficulty managing their interactions, and thus swim farther away from other individuals in their group and face a different way; control groups with no lesioned members would show no such effect.

1-F-179 *Are sung words better recognized than spoken words?*

Agnès Zagala[1], Séverine Samson[2]

[1]International Laboratory for BRAin, Music and Sound Research, [2]Neuropsychology and Audition team Laboratory PSITEC EA 4072

Even though it is widely agreed that music is an excellent memory support of verbal information, the mechanism underlying this phenomenon remains quite unknown. In this behavioral study, we analysed the differences between recognition memory of sung or spoken words. We have set up a protocol including sung or spoken words memorisation, distributed in several presentation and memory tests (item recognition - word itself, then context recognition - if it was sung or spoken) to focus on memorization dynamics. Thirty-nine healthy French participants accepted to take part of the experiment. During the first session we presented them the first list of words, then during the second session (twelve hour later) we presented them the second list of words, a reactivation of both lists, and memory tests. We divided them into two groups: those having a night sleep during the twelve hour delay and those having a regular waking day. We have shown that item and associated context recognition scores are significantly higher for sung words than spoken words. Furthermore, we observe a significant performance improvement for item as well as context recognition when participant slept between the item presentation and the memory test. This results show that adding associated information such as context to a verbal task, and sleeping during the learning phase can have a significantly positive effect on recognition memory.

1-F-180 *Quail-ure: a tale of an animal that can't do anything*

Josephine Esposto[1], Chelsey Damphousse[1]

[1]Wilfrid Laurier University

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In order to be able to navigate and carry out desired behavioural responses to reach a goal, it is necessary to have an on-going representation of the environment. Lead by the discovery of place cells, research to date has identified several different types of spatially tuned cells within both the mammalian and avian hippocampus. For social animals, not only is the representation of food, shelter and nesting locations vital for survival, but the location of conspecifics also carries important information. Where a conspecific is within an environment represents many opportunities, including but not limited to, mating and social learning. By using quail as a model species, we tested the limits of their social recognition abilities by first following a procedure mimicking those used traditionally for spontaneous object recognition; however instead of using objects we utilized conspecifics within a novel arena (familiar vs. non-familiar and recent vs. non-recent). Our behavioural findings thus far in combination with existing literature on mate-choice selection suggest that quail are capable of conspecific recognition. These findings represent preliminary, encouraging results as we approach our goal of identifying where social information is represented within the avian HF via catFISH and electrophysiological methods.

1-F-181 *Interactions between medial prefrontal cortex and mediodorsal thalamus are necessary for performance of the odour span task in rats*

Gavin Scott[1], Max Liu[1], Nimra Tahir[1], Nadine Zabder[1], Yuanyi Song[1], Quentin Greba[1], John Howland[1]

[1]University of Saskatchewan

Working memory (WM), the capacity for short-term storage of small quantities of information for immediate use, is commonly thought to depend on persistent neural activity within the prefrontal cortex. Recent evidence indicates that the prefrontal neuronal activity supporting WM is driven by thalamocortical connections arising in mediodorsal thalamus (mdThal). However, the role of these connections has not been studied using olfactory stimuli, leaving open the question of whether this circuit extends to all sensory modalities. Moreover, manipulations of the mdThal in olfactory memory tasks have yielded mixed results. In the present experiment, we investigated the role of connections between the rat medial prefrontal cortex (mPFC) and mdThal in the odour span task (OST) using a pharmacological contralateral disconnection design. Inactivation of the mPFC alone impaired mean span capacity replicating previous findings. Inactivation of the mdThal also significantly impaired mean span while also increasing response latency, confirming that the mdThal plays an essential role in performance of the OST. Finally, contralateral disconnection of the mPFC from the mdThal significantly impaired mean span and increased latency. The results provide evidence that the thalamocortical circuit connecting the mPFC and mdThal also plays a critical role in olfactory WM in addition to WM in other sensory modalities.

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1-F-182 *Dose dependent acute alcohol exposure affects free swimming behaviour of wild type zebrafish fry*

Benjamin Tsang[1], Rida Ansari[1], Robert Gerlai[1]

[1]University of Toronto

The ease of environmental manipulation, practical simplicity, and high enough system complexity of the zebrafish make it a particularly tractable model for phenomics and behavioral neuroscience. In particular, the zebrafish has proven to be a valuable tool for modelling the effects of alcohol induced brain and behavioral abnormalities. In the current study, we utilize 6-8 post-fertilization day old larval zebrafish (fry) to explore the effects of a 40 min-long immersion in an alcohol bath containing 0, 0.5 and 1% v/v alcohol. We test the fish in six 3.5cm well plates, a significantly larger arena than the conventional 96-well plates used in most pharmacological screens with zebrafish larvae. The increased area of the test arena allows higher sensitivity to detect alterations in behavior. For example, we found the intermediate dose of alcohol (0.5%, vol/vol) to exert a stimulant effect demonstrated by increased swim speed, turning, temporal variability of swim speed and turning, and diminished frequency of staying immobile. We also found the high dose of alcohol (1%) to elicit an opposite response, a sedative effect. This biphasic dose response of alcohol mimics what has been found in mammals, including humans, and thus we conclude that a few day-old zebrafish fry may be a cost effective and efficient tool with which one can screen for small molecules with alcohol-effect modifying properties.

1-F-183 *Assessment of cognitive performance in Dp(16)1/Yey/+ mouse model of down syndrome*

Negin Rezaie[1], Brian Bennett[1]

[1]Queen's University

Down syndrome (DS, trisomy 21) is the most common autosomal aneuploidy, with an incidence of about 1 in 800 live births. DS greatly increases the risk of Alzheimer's disease (AD), and most individuals with DS develop AD neuropathology by age 40. Our objective was to determine whether the working and spatial memory impairments seen in AD and in AD mouse models are also present in the Dp(16)1/Yey/+ (Dp16) mouse model of DS. In this model, the entire Hsa21 orthologous region on Mmu16 (~119 genes), has been duplicated and added onto the distal portion of one of the endogenous Mmu16 chromosomes. We assessed recognition memory using the novel object recognition (NOR) task, spatial working memory by the Y-Maze task and spatial reference memory using the Morris Water Maze (MWM) task. Behavioural testing was performed bimonthly in Dp16 mice and age-matched WT littermates beginning at 2 months of age. In the

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NOR and Y-maze tasks, Dp16 mice demonstrated a progressive decrease in performance in both memory tasks compared to WT mice. In the MWM task, there were no differences in swim speed between Dp16 and WT mice or in latency times for cued platform training, whereas latency times for Dp16 mice were significantly longer in hidden platform trials. In probe trials, Dp16 mice spent less time and had fewer crosses into the target quadrant than WT mice. The Dp16 DS mouse model may thus represent a useful comparator to current AD mouse models for the assessment of pharmacological interventions designed to improve cognitive performance in humans with DS and/or AD.

1-F-184 *Acute Caffeine Exposure on Larval Zebrafish*

Mahrukh Iqbal[1], Benjamin Tsang[2], Robert Gerlai[2]

[1]UTM, [2]University of Toronto

Anxiety disorders are one of the most prevalent subgroup of mental disorders that are distressing and disabling in nature, and represent a large unmet medical need. Zebrafish represent a great model to study the effects of anxiolytic properties as they present an ideal balance between system complexity and practical simplicity, translational relevance and applicability to high throughput behavioural drug screens. Zebrafish is at the vanguard of pharmacological behavioural research, and thus characterizing its profile is important. Caffeine in high doses exhibits anxiogenic properties and its administration to zebrafish may serve as a positive control in psychopharmacology research. The current study employed caffeine to be immersed in 7-8 days old zebrafish post-fertilization in 0, 25, 150, or 400 mg/L caffeine solution for 40 minutes, and measured the behavioural responses of the fish using automated video tracking. It was hypothesized that reduced activity at the highest dose may be due to anxiogenic effects whereas the increased activity at the medium dose to the stimulant actions of caffeine.

1-F-185 *Dissecting the corticothalamic plasticity mechanisms underlying visual recognition memory in mice and humans*

Peter Finnie[1], Aurore Thomazeau[1], Dustin Hayden[1], Lara Pierce[2], Ying Li[3], Maia Lee[3], Ming-fai Fong[1], Charles Nelson[2], Samuel Cooke[4], Mark Bear[1]

[1]Massachusetts Institute of Technology, [2]Boston Children's Hopital/Harvard Medical School, [3]Wellesley College, [4]King's College London

The neocortex is arranged into 6 cell layers that undergo life-long experience-dependent plasticity, but it is unclear how this contributes to memory storage. Mice repeatedly exposed to an oriented visual grating stimulus exhibit a simple form of visual recognition that depends on

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lasting plasticity in primary visual cortex (V1). Over days of familiarization to the stimulus, a stereotyped behavioural response undergoes gradual orientation-selective habituation (OSH). Concurrently, the magnitude of visually-evoked potentials recoded in V1 undergoes stimulus-selective response potentiation (SRP). N-methyl-D-aspartate (NMDA) receptors in V1 excitatory neurons are necessary for both processes, suggesting that OSH and SRP share a common mechanism. Here we use an intersectional transgenic approach to systematically knock out NMDA receptors from principal cells in each cortical layer. Surprisingly, OSH is disrupted only when NMDA receptors are knocked out in L2/3, but this has minimal impact on SRP. Conversely, SRP is impaired only in mice lacking NMDA receptors in L6 cells, and although short-term behavioural habituation is abnormal, long-term OSH is intact. Our emerging model posits that multiple habituation systems may interact to control behavioural output. We will also discuss ongoing efforts to translate these assays to human populations for use as biomarkers of neurodevelopmental variation.

1-F-186 *Volitional control of individual neurons in the human mesial temporal lobe using intracranial neurofeedback*

Kramay Patel[1], Chaim Katz[1], Ryan Ramos[1], Milos Popovic[2], Taufik Valiante[3]

[1]University of Toronto, [2]University Health Network, [3]Krembil research Institute, University Health Network

Background: Neurofeedback, which refers to training individuals to control their neural activity using sensory feedback, has been investigated as an alternative treatment for medically refractory epilepsy (MRE). Typically, the source of neural activity for neurofeedback is scalp electroencephalography (EEG) which lacks adequate spatial specificity. For many patients with MRE, seizures often originate from highly localized regions which cannot be effectively targeted with conventional neurofeedback protocols. Methods: In the present study, we extracted single-unit activity from deep brain structures in six epilepsy patients undergoing pre-surgical evaluation. We used this activity in a novel, low-latency neurofeedback task, in which we trained these patients to upregulate the activity of a randomly selected neuron, or a small ensemble of neurons in mesial temporal lobe structures. Results: Our preliminary results show that most participants (5/6) were able to reliably upregulate the firing rate of the selected neuron or ensemble of neurons. One of these participants, who was trained to upregulate and downregulate the firing rate of the selected neuron in alternate trials, was also able to do so reliably, showing significantly higher firing rates in the upregulation trials when compared to the downregulation trials following training. Conclusion: This study demonstrates the feasibility of intracranial neurofeedback and lays the groundwork for future work in investigating its use in treating neurological conditions such as epilepsy.

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1-F-187 *Development and evaluation of a liposomal formulation of Allium cepa extract for the management of ischemia reperfusion induced cerebral injury in mice*

Varinder Singh[1], Pawan Krishan[2], Richa Shri[2]

[1]Maharaja Agrasen University, [2]Punjabi University, Patiala, Punjab, India

Oxidative stress is a major trigger in ischemia reperfusion (I-R) induced cerebral injury. Thus, drugs with antioxidant properties are being investigated for the treatment of cerebral I-R injury. Antioxidant mediated neuroprotective effects of ethyl acetate fraction (EF) from Allium cepa extract are reported previously. The present study elaborates the development and optimization of a liposomal delivery system for EF with an objective of increasing its brain bioavailability and reducing the dose. Liposomal formulation (LF) was prepared by thin film hydration method and optimised with respect to particle size, encapsulation efficiency (EE), zeta potential, morphology (TEM) and physical stability. Bilateral common carotid artery occlusion method was used to induce cerebral I-R injury in mice. Animals with I-R injury were treated with LF via intra-nasal route for 7 days. Cognitive and sensorimotor functions, cerebral infarct size and brain oxidative stress were determined to corroborate the neuroprotective effects of LF. Optimised LF showed formation of nano-sized stable spherical vesicles with high EE and anionic zeta potential. Biological evaluation of LF showed significant improvement of cognitive and sensorimotor functions, reduction in cerebral infarct size and brain oxidative stress. These effects were similar to those produced after oral administration of EF, but at 1/10th the oral dose. The present study showed successful development of neuroprotective liposomal formulation for EF which may be developed for clinical use after further necessary investigations.

1-F-188 *Effects of anxiolytic drug buspirone HCl on the behaviour of juvenile zebrafish (Danio rerio)*

Anamika Bhattacharjee[1], Ajandan NandaKumar[1], Robert Gerlai[2]

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

Avoidance of aversive stimuli has high fitness value in the animal kingdom; however, the mechanism underlying such responses is not well understood. Using a psychopharmacology approach one can analyze the neurobiological mechanisms of fear and anxiety. The zebrafish is one of the simplest laboratory vertebrate species amenable to the analysis of such processes. Due to their evolutionary conservation, zebrafish have been found to respond to human drugs in predicted ways. Prior studies have demonstrated that adult and larval zebrafish exhibit reduced anxiety in response to anxiolytics. However, the effects of Buspirone HCl, an anxiolytic drug used in the clinic, are controversial. Using juvenile zebrafish, we studied the dose response to Buspirone. Zebrafish were exposed to one of three concentrations (5, 20, or 80 mg) for 1 hour, and their behavior recorded during this period. The recordings were analyzed using Ethovision

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XT tracking software. A significant dose-dependent increase of the frequency of immobility was found, without significant alteration of total duration of immobility and without any alternation of other swim path parameters. These results are inconsistent with behavioral changes expected in the case of reduced anxiety, which typically include a reduction of duration of immobility, erratic movement, and variability of swim speed. We propose further examination of the behavioral effect profile of Buspirone, using multiple different fear/anxiety paradigms and analysis of neurobiological mechanism.

1-F-189 *Deep learning to prove the existence of qualia*

Mahboobeh Parsapoor[1]

[1]McGill University

One of the significant challenges in the field of cognitive neuroscience is the verification of the existence of qualia. , which has been the source of conflicts between cognitive neuroscientists. We believe extraordinary features of our cognition. In the era of artificial intelligence (AI) in particular advanced and powerful machine learning tools such as and deep learning methods, we can prove the existence of qualia. To do so, we will set up some experimental studies by focusing on evoking emotional responses of participants and record their brain activities such as electroencephalogram (EEG). Then we examine deep learning to detect qualia and its effect on brain activities. Our research aims to speed up studies in the AI community that have focused on creating artificial consciousness.

1-F-190 *Explore the ameliorative potential of Ficus benjamina in hyperalgesia through the modulation of nitric oxide and KATP channel in mice*

Amrit pal Singh[1]

[1]Guru Nanak Dev University

Objective: The study was aimed to explore the potential of extract of Ficus benjamina in chemical induced hyperalgesia and carrageenan induced inflammation. The role of nitric oxide modulation in the observed effect was explored. Methods: Male swiss albino mice in the weight range of 25-30 g were used for the experimentation. Hyperalgesia was induced by an intraplantar injection of formalin in the right hind paw. Inflammation was induced on injection of carrageenan into the plantar side of right hind paw. Acute toxicity studies were carried out as per the OECD guidelines. Results: Hyperalgesia in the neurogenic and inflammatory phases of formalin administration was significantly reduced. L- arginine and glipizide reversed this effect of the extract. Maximum inhibition of paw edema was observed after 3 hours of carrageenan injection to the treated mice.

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The acute toxicity study did not reveal any toxicity. Conclusion: The study advocates the analgesic and anti-inflammatory properties of the plant. Inhibition of nitric oxide pathway and K+ATP channels opening are the suggested mechanisms underlying the response.

1-F-191 *Forming false memories: excitability-dependent incorporation of neutral stimuli into a fear memory.*

Jocelyn Lau[1], Asim Rashid[2], Sheena Josselyn[1]

[1]University of Toronto, [2]The Hospital for Sick Children

Memory is often thought of as being an immutable and accurate recollection of events. However, psychology experiments investigating false memories in humans have demonstrated the mutability of memories. Previous research in mice has shown that cued fear memory formation (CS1 [2.8 kHz tone] + shock) triggers a transient (<6h) increase in neuronal excitability in the lateral amygdala (LA) such that formation of a subsequent fear memory to a distinct stimulus (CS2 [7.5 kHz] + shock) results in co-allocation of the two memories to these more excitable LA neurons. Here, we ask whether mere exposure to a neutral stimulus (CS2 in the absence of shock) shortly after a fearful event (3h) can cause incorporation of the neutral stimulus into the fearful memory. Results show that exposure to CS2 3h, but not 24h, after fear conditioning to CS1 successfully incorporated experience of the previously neutral CS2 into the fearful memory, as demonstrated by a freezing response to CS2 in a memory recall test. To investigate whether this effect is excitability-dependent, a herpes simplex virus encoding both channelrhodopsin-2 (ChR2-H134R) and halorhodopsin (NpHR3.0) was injected into the LA to bidirectionally control neurons allocated to the fearful memory. Inhibition of allocated neurons during CS2 exposure at 3h and excitation of these neurons during CS2 exposure at 24h reversed seen effects, suggesting an excitability-dependent phenomenon. These results shed light on the temporal properties of memory and suggest that recently formed memories may be open to alteration.

1-F-192 *Silencing a monosynaptic projection from the basolateral amygdala to the ventral hippocampus reduces appetitive and consummatory alcohol drinking behaviors*

Sarah Ewin[1], Jeff Weiner[1]

[1]Wake Forest School of Medicine

Alcohol use disorder (AUD) and anxiety disorders frequently co-occur and this dual diagnosis represents a global health and economic burden. Although many studies have implicated basolateral amygdala (BLA) hyperexcitability in the pathogenesis of AUD and comorbid conditions, little is known about the specific BLA circuits that contribute to these disorders. The

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BLA sends a strong monosynaptic excitatory projection to the ventral hippocampus (vHC) and optogenetic manipulation of this circuit regulates anxiety-related behaviors. Whether this pathway influences alcohol drinking is not known. Here, we employed a rodent operant drinking regimen that procedurally separates appetitive (seeking) and consummatory (intake) behaviors, chemogenetics, and brain region-specific microinjections, to determine if the BLA-vHC circuit influences alcohol drinking-related behaviors. We first confirmed that chemogenetic silencing of this circuit reduced anxiety measures. We then demonstrated that inhibiting the BLA-vHC pathway significantly reduced both appetitive and consummatory alcohol drinking behaviors. Sucrose seeking and intake were also reduced, albeit to a lesser extent than alcohol drinking measures. Together, these findings provide the first indication that a BLA-vHC circuit may regulate both appetitive and consummatory alcohol drinking behaviors and add to a growing body of evidence suggesting that dysregulation of this pathway may contribute to the pathophysiology of AUD and anxiety/stressor-related disorders. Supported by AA25819 (SEE); AA26117, AA17531, AA26551, AA26551 (JLW).

1-F-193 *AdipoRon ameliorates streptozotocin-induced impairment in cognitive impairment and adult hippocampal neurogenesis*

Sonata Yau[1], Thomas Ho Yin Lee[1], Brian R Christie[2]

[1]Hong Kong Polytechnic University, [2]University of Victoria

Background:Diabetic patients have an increased risk for having cognitive impairment and developing depression. Physical exercise is an effective therapeutic for cognitive impairment such as depression and dementia. Cognitive impairment is often associated with neuronal loss and reduced synaptic plasticity in the brain. Our previous work has demonstrated that adiponectin is a key mediator for exercise-induced adult hippocampal neurogenesis. Recently, AdipoRon, an adiponectin receptor agonist, is effective in treating diabetes in mouse model. Here we sought to examine whether AdipoRon could restore impairment in learning and memory, and adult hippocampal neurogenesis associated with diabetes. Methods:Six-week old diabetic and control C57BL6/J male mice received 20 mg/kg AdipoRon or voluntarily wheel running continuously for two weeks, followed by open field test, Y-maze test to anxiety and learning and memory performance. Immunohistochemical analysis with cell proliferation marker: Ki67 and immature neuronal marker: doublecortine was performed to examine changes of hippocampal adult neurogenesis. Results:Our behavioural test results demonstrated that both AdipoRon and exercise restored spatial recognition memory deficit in diabetic mice. These behavioural benefits were associated with enhancement in cell proliferation in the hippocampal dentate gyrus. However, AdipoRon did not mimic the effect of exercise on promoting survival and neuronal differentiation in diabetic mice. Conclusion:Our data suggested that chronic administration with AdipoRon is effective in promoting learn

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1-F-194 *Lateral hypothalamus is a central hub for motivated response*

Ekaterina Martianova[1], Alicia Pageau[1], Danahé LeBlanc[1], Christophe Proulx[2]

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

The lateral hypothalamus (LHA) sends neural outputs to brain regions known to control reward and motivated behaviors. However, how these distinct LHA outputs process information to control behavior is poorly known. Here, we use in vivo fiber photometry calcium (Ca2) imaging to characterize LHA outputs in freely moving mice. An AAV encoding the calcium indicator GCaMP6s was injected in the LHA, and optic fiber cannulas were implanted to target three major downstream LHA targets: the lateral habenula (LHb), the ventral tegmental area (VTA), and the dorsal raphe nucleus (DRN). This allowed to record neural activity simultaneously and specifically at LHA-LHb, LHA-VTA, and LHA-DRN pathways, in mice subjected to different stimuli or placed in different contexts. Ca2 signals in three LHA outputs increased when mice were presented with aversive airpuffs and decreased during rewarding sucrose consumption. We found a significant correlation between Ca2 signals and mobility scores in mice free to explore an open field or during tail-suspension test (TST). The correlation was significantly higher during TST suggesting that LHA may guide motivated responses in stressful contexts. This assertion was supported by an increased correlation between Ca2 signals and mobility scores after administration of cued foot-shocks. Combined, our results suggest that the LHA may be a central hub of emotion processing to the LHb, VTA, and DRN to motivate proper behavioral responses when an animal is high state of vigilance.

1-F-195 *Novel negative allosteric modulator (NAM) of Cannabinoid Receptor 1 (CB1) ameliorates symptoms due to dopamine dysregulation in psychiatric disorders.*

Catharine Mielnik[1], Iain Greig[2], Mostafa Abdelrahman[2], Laurent Trembleau[2], Ali Salahpour[1], Amy Ramsey[1], Ruth Ross[1]

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

The prevalence of psychiatric disorders is common, schizophrenia reporting a prevalence rate of ~1% respectively. Dopamine controls cognitive, emotional and motor aspects of goal-directed behaviour; alterations in dopamine play a role in a number of psychiatric disorders. The endocannabinoid systems serves as an important filter of afferent inputs, helping shape how incoming information is conveyed onto dopamine neurons and to output targets. Therefore, we hypothesize that compounds negatively targeting the endocannabinoid system could be candidates in treating positive and affective symptoms in psychiatric illness. We tested the effect of ABM300, a novel negative allosteric modulator (NAM) of the CB1 receptor (IC50 of ~20nM).

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GluN1KD and DATKO mice display hyperactivity, impaired habituation and sensorimotor gating, with increased stereotypy and vertical activity, in a state of mania-like behaviour. Following acute treatment with ABM300 (10mg/kg), amelioration of these behaviours was observed. GluN1KD and DATKO saw a reduction in locomotor and vertical activity, along with an amelioration of repetitive stereotypic movements and mania-like behaviour. DATKO also saw additional amelioration of sensorimotor deficits. The data suggest that CB1 NAMs (specifically ABM300) represent a novel treatment for psychiatric symptoms as a result of dopamine dysregulation. Furthermore, targeting the endocannabinoid system offers the opportunity to normalize deficits that arise from differing underlying dysfunctions that manifest as similar behavioural changes.

1-F-196 *Strange human visual perception on physical world veracity*

Tajnin Mohammad Hashim[1], Ganesh Elumalai[1], Anjana Chowdary Elapolu[1], Christina Vadiyala[1], Nanduri Mojess Vamsi[1], Harshita Catherine[1], Nicolas Henrique Ceresoli[1]

[1]Team NeurON - Texila American University

A prodigious sense of 'vision' is a cognitive calibre through which a human perceives the physical world. The apprehension of what and how we view the reality through the eyes is visual perception. Brain processes what our eyes congregates, constructing a perception that sometimes, doesn't sit parallel with the reality. The brain has a quirk of assisting in a peculiar way of perceiving the subjective physical reality of the objective state, even when there's no creation of illusion by the object. The rigor in identifying and stationing objects by sight provokes by the rise in intricacy and abundance of the items in the field of vision and by transience of luminance. Even after several attempts on solving the theories behind such perceptions, our knowledge on them is still insubstantial. The enigma behind some baffling aspects of human visual perceptions, like colour, luminance, line, distance and depth are attempted to be abridged. Consolidation of various parameters of discernment leads to perception of an object. Our analysis focuses on akin parameters, such as - psychological, physiological, interpretational, empirical and neurological. We focused on the factors which commerce in order to convey outputs different from reality under different conditions, and why our judgment is challenged by moderate contrast in the framework of our field of view, and highlight the effect of visual perceptions in clinical complications like Alzheimer's and Parkinson's patients, which relies on comparative analysis. Keywords: Visual perception, Alzheimer's, Parkinson's, physical reality

1-F-197 *Exposure to heroin and heroin paired context enhance consolidation of object memory in rats*

Andrew Huff[1], Michael Wolter[1], Nana Baidoo[1], Boyer Winters[1], Francesco Leri[1]

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[1]University of Guelph

The memory enhancing hypothesis of drugs of abuse proposes that drugs promote addictive behaviours through facilitation of memory consolidation processes. Because addictive behaviours are also profoundly affected by environmental stimuli paired with the effects of drugs, it is possible that drug conditioned stimuli can also impact memory consolidation processes. The current study tested this hypothesis by comparing the effects of immediate and delayed post-training exposure to heroin to immediate and delayed exposure to a heroin-paired context (CS+), on spontaneous object recognition (SOR) memory. Four within-subject experiments were performed in Sprague-Dawley male rats demonstrating that: 1) immediate, but not delayed, post-training administration of heroin (0.3 and 1 mg/kg) enhanced SOR; 2) rats displayed a hyperlocomotion response when tested drug free in a context that was repeatedly paired with the effects of 1 mg/kg heroin (CS+); 3) immediate, but not delayed, post-training confinement to the heroin CS+ enhanced SOR; and 4) the effect of the CS+ on SOR memory was more resistant to extinction than the effect of the CS+ on locomotion. Taken together, these findings in rats indicate that a heroin-paired context has multiple effects on behavior and that, similarly to heroin itself, it can impact memory consolidation processes.

1-F-198 *Cholinergic system involvement in reactivation-induced object memory updating in a newly developed memory modification task*

Kristen Jardine[1], Cassidy Wideman[1], Chelsea MacGregor[1], Krista Mitchnick[1], Boyer Winters[1]

[1]University of Guelph

Memory traces can be reactivated by retrieval, rendering the memory labile for some time afterwards. Reactivated memories can be erased or strengthened, but there is limited research of the mechanisms underlying other forms of memory modification. We propose that acetylcholine (ACh) facilitates memory updates due to its role in object memory destabilization. Intra-perirhinal cortex muscarinic ACh receptor 1 (M1) agonism appears to trigger a cellular cascade that results in the destabilization required for retrieval-induced object memory erasure. M1 receptors may also initiate more subtle forms of retrieval-induced memory updates, but this has not been systematically tested due to the lack of a validated rodent model. The present study addresses this gap by developing a memory modification task in which rats' object memories are reactivated immediately prior to exploration of an alternate empty context. On test day, rats explore the sampled objects less when they are in the same alternate context as the reactivation phase compared to a different alternate context; thus, the object-context combination appears to be treated as familiar only when the context is presented following object memory reactivation. Furthermore, pre-reactivation systemic scopolamine blocks this apparent memory update, consistent with our past findings that M1 receptor activation is required for object memory

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destabilization. These results therefore support our hypothesis that M1 receptor functioning is required for retrieval-induced qualitative memory modification.

1-F-199 *Functional integration of adult-generated granule cells in the avian hippocampal formation*

Diano Marrone[1], Chelsey Damphousse[1]

[1]Wilfrid Laurier University

Adult neurogenesis of granule cells (GCs) is a key mechanism of structural plasticity in the hippocampal dentate gyrus, a subregion that is critical for proper memory function in the face of high similarity between items of information to be remembered. Although it is known that birds also generate new GCs throughout life, this process is modulated by experience, and ablating these cells causes memory deficits, our knowledge could be furthered by tracking the activity of newly-born GCs during behavior. As a critical intermediate point towards this goal, here we establish the timecourse by which GCs integrate and become active (i.e., express activity-dependent Egr1, a reliable reporter of activity in individual neurons) during spatial behavior. Groups of Japanese quail were injected with 100mg/kg BrdU and then remained in their colony room for a period of 1, 2, 3, 4, 5, 6, or 7 weeks. Following each delay, birds explored a novel environment to engage GC activity, and were then sacrificed and the tissue was analyzed using immunohistochemistry for NeuN, BrdU, and Egr1. These data will map the progression of neurogenesis in the avian hippocampus and reveal the optimal timing for examining the activity of these cells in further experiments.

1-F-200 *Genome-wide association study (GWAS) of word reading: overlap with risk genes for neurodevelopmental disorders*

Kaitlyn Price[1], Karen Wigg[2], Yu Feng[2], Kirsten Blokland[3], Margaret Wilkinson[3], Gengming He[3], Elizabeth Kerr[3], Tasha-Cate Carter[3], Sharon Guger[3], Maureen Lovett[3], Lisa Strug[3], Cathy Barr[2]

[1]University of Toronto, [2]University Health Network, [3]The Hospital for Sick Children

Reading disabilities (RD) is a neurocognitive disability characterized by difficulties with accurate/fluent word recognition, poor spelling, and decoding abilities. Comorbid psychiatric disorders are common in children with RD and impact academic achievement and social development. RD is a genetic trait, but limited published GWAS exist. We performed a GWAS for a measure of word reading using a family based sample selected for reading difficulties from Toronto and a population based sample from Philadelphia (Philadelphia Neurodevelopmental Cohort). The final analysis after quality control was performed with >5 million single nucleotide

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polymorphisms (SNPs) on 5054 subjects. The analysis did not identify genome-wide significant results, however results near significance, indicate overlap for genes previously identified in GWAS for educational attainment and for neurodevelopmental disorders, particularly autism spectrum disorder (ASD). ASD was an exclusion criterion for the Toronto sample, thus the overlap with autism suggests shared genetic risk for ASD, possibly for shared genetic contributions to language difficulties. Polygenic Risk Scores (PRS) were used to quantify genetic overlap and significant results were found for word reading and educational attainment, intelligence and attention-deficit/hyperactivity disorder. PRS for word reading and ASD did not reach significance because ASD associated variants are rare or copy number variants that are excluded in GWAS analysis. The genetic overlap between these disorders suggests common etiological pathways amongst disorders.

1-F-201 *Effects of optogenetic activation of the basolateral amygdala on the response to a reward cue*

Alice Servonnet[1], Giovanni Hernandez[1], Pierre-Paul Rompré[1], Anne-Noël Samaha[1]

[1]Université de Montréal

A cue associated with reward delivery (conditioned stimulus, CS) can gain both predictive and incentive motivational values. CS can then elicit attention and direct behavior. Here, we assessed the effects of optogenetic stimulation of basolateral amygdala (BLA) neurons on the predictive and incentive motivational effects of a CS. Through Pavlovian conditioning, water-restricted rats learned that a compound cue (light-tone) predicts water delivery. During acquisition, some rats received stimulation of BLA ChR2 paired or unpaired with CS presentation and some rats received no stimulations (controls). Paired but not unpaired stimulation of BLA ChR2 enhanced CS predictive value. We then assessed incentive motivation for the CS in an operant task where rats could lever-press for the CS alone. Controls pressed more on the active lever (CS presentation) than the inactive lever (no CS), indicating the CS has motivational value. Rats that received BLA ChR2 stimulations during acquisition, paired or unpaired with the CS, did not discriminate between the levers, indicating no incentive motivation for the CS. Controls then received BLA ChR2 stimulation paired with CS presentations during operant responding for the CS. This enhanced its incentive motivational value. Finally, rats did not lever-press for BLA laser stimulation alone, suggesting it is not intrinsically rewarding. Thus, increasing BLA neuronal activity influences both the predictive and motivational effects of CS. Future studies should investigate different BLA-dependent circuits that might regulate these CS effects.

1-F-202 *The histone chaperone Anp32E regulates H2A.Z eviction and turnover and regulates memory formation in the hippocampus*

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gilda stefanelli[1], Mark Brimble[2], Klotilda Narkaj[1], Anas Reda[3], Andrew Davidoff[2], Brandon Walters[4], Iva Zovkic[1]

[1]University of Toronto Mississauga, [2]St. Jude Research Hospital, [3]Bates college, [4]The Hospital for Sick Children

H2A.Z is a variant of histone H2A, whose role as a memory suppressor we recently discovered. H2A.Z is removed from chromatin after learning and AAV-mediated H2A.Z depletion results in enhanced memory, suggesting that H2A.Z removal promotes memory formation. However, the molecular mechanism underlying learning-induced H2A.Z removal remains uncharacterized. Anp32E was recently identified as an H2A.Z-specific histone chaperone that removes H2A.Z from nucleosomes, leading us to hypothesize that Anp32E-mediated removal of H2A.Z is crucial for memory formation. Here, we show that Anp32E and H2A.Z are simultaneously bound to several H2A.Z-enriched genes in the mouse hippocampus. In response to fear conditioning, H2A.Z and Anp32E are concurrently evicted from sites in which they co-localize. Moreover, Anp32E is functionally relevant for memory formation, as AAV-mediated knock-down of this chaperone in the hippocampus results in impaired memory, whereas Anp32E overexpression results in enhanced memory. Notably, manipulating Anp32E levels in cultured neurons results in altered expression of H2A.Z-regulated genes and altered accumulation of H2A.Z in different chromatin fractions. Moreover, knock-down of Anp32E in primary neurons results in impaired dendritic branching. Strikingly, simultaneous knock-down of Anp32E and H2A.Z results in rescue of altered gene expression, impaired dendritic branching and memory formation seen in Anp32E knock-down. Overall, our data suggest that Anp32E is a functional component of the molecular machinery regulating H2A.Z eviction in neurons.

1-F-203 *Decreased corticostriatal coherence and locomotion in rats following acute exposure to vapourized delta-9-tetrahydrocannabinol*

Bryan Jenkins[1], Tapia Foute Nelong[1], Sam Creighton[1], Boyer Winters[1], Melissa Perreault[1], Jibran Khokhar[1]

[1]University of Guelph

Introduction: Over 14% of Canadians use cannabis, with nearly 60% of these individuals reporting daily or weekly use. Little is known about the differential effects of varying routes and frequency of cannabis use on brain and behaviour. In this study, we assessed changes in neural circuit dynamics and behaviour in rats exposed to vapourized ∆-9-tetrahydrocannabinol (THC). We hypothesized that THC would reduce coherence between brain regions and lead to an increase in anxiety-like behaviours. Methods: Sprague-Dawley rats were implanted with electrode arrays targeting the prefrontal cortex (PFC), orbitofrontal cortex (OFC), ventral hippocampus (vHIP), and dorsal striatum (dStr). Rats were administered THC using a Volcano® vapourizer and their

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behaviour assessed in an elevated plus maze. Results: Decreased power was observed in the dStr and the PFC (70-90 Hz range, high gamma). Decreased coherence was observed between the dStr and cortical regions (40-50 Hz range, low gamma), and the vHIP and PFC (0-5 Hz range, delta/low theta), after THC administration. THC-treated rats showed a decrease in closed arm entries and distance travelled in the elevated plus maze compared to vehicle-treated rats. Interestingly, time spent in the closed arm did not differ between treatment groups. Conclusion: Vapourized THC exposure led to acute behavioural and neurophysiological changes consistent with some of the known effects of cannabis. In addition, our results highlight the need to consider the suppression of locomotion by cannabis when designing behavioural studies based on locomotion.

1-F-204 *Sex-specific signatures of stress susceptibility in the glutamatergic projections from the ventral hippocampus to nucleus accumbens*

Jessie Muir[1], Rosemary Bagot[1]

[1]McGill University

Epidemiological data indicates stress is a major factor risk factor associated with development of depression, yet not everyone reacts to stress the same way. Certain factors, such as biological sex and early life adversity, can increase risk for depression. Understanding the mechanisms underlying this increased vulnerability is essential for targeted treatment and, ultimately, prevention. In previous work we identified pre-existing differences in nucleus accumbens (NAc) activity associate with resilience to chronic social defeat stress (CSDS), an animal model for depression, indicating baseline activity may influence future susceptibility even in the absence of other identified risk factors. Using fiber photometry, a technique for probing in vivo calcium neuronal activity in freely moving mice, we recorded calcium transients in the glutamatergic inputs from the ventral hippocampus (vHIP) to the NAc during standard tests of depressive-like behavior before and after chronic variable stress (CVS), another model for depression which is readily adaptable to males and females. Stimulation of this pathway following stress has previously been shown to increase susceptibility to CSDS. Our findings identify interesting sex-specific differences in this pathway that may predict behavioral adaptation following CVS.

1-F-205 *Visualizing an amygdala engram*

Emily Kramer[1], Patrick Steadman[1], Alexander Jacob[1], Albert Park[1], Paul Frankland[1], Sheena Josselyn[1]

[1]University of Toronto

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An engram or memory trace is the neural substrate representing a past experience and can drive future behaviour. While engrams may be localized across many regions of the brain, the amygdala in particular is known to be critical for the encoding and storing of associative memories. However, the process by which neurons are recruited to a specific engram in the amygdala are not well known. We investigate both the proportion and spatial distribution of Arc+ neurons (putative engram neurons) across the entire amygdala following memory recall using a novel 3D imaging and data processing pipeline. We use a modified iDISCO protocol to clear lipids from the brains of animals who recall an aversive or appetitive experience, and stain for Arc protein as a marker of neuronal activity. Using light sheet microscopy, we image the nuclei and Arc signal of across the entire intact amygdala (without need for reconstruction). After registering and segmenting these images, we are able to produce a complete picture of Arc+ cells in the amygdala (including its many nuclei) at the time of memory recall. Initial analysis has confirmed the the lateral amygdala, in particular, is more active following the recall of an aversive memory, compared to an appetitive memory or no recall controls. Interestingly, analysis of the distribution of Arc+ cells in the lateral amygdala of recall animals shows a non-random level of clustering, suggesting that those neurons recruited for memory recall may not be completely randomly distributed in the lateral amygdala, for both aversive and appetitive experiences.

1-F-206 *Using a novel conflict paradigm to understand the role of the medial temporal lobe in approach-avoidance conflict decision-making and outcome uncertainty*

Sonja Chu[1], Cendri Hutcherson[1], Rutsuko Ito[1], Andy Lee[1]

[1]University of Toronto

Medial temporal lobe regions have been implicated in the processing of learned approach-avoidance (AA) conflict but it is unclear if these structures are responding to conflict (i.e. opposing motivations and outcomes) or uncertainty (i.e. varying likelihood of outcome occurrence). To investigate this, 24 neurologically healthy participants first learned to approach or avoid novel visual objects that were positive, negative, or neutral with the goal of maximizing reward and minimizing punishment. Approaching a positive object led to a reward, approaching a negative object led to a punishment, and both approaching a neutral object and avoiding any object resulted in no outcome. Following successful learning, subjects were presented with pairs of these objects during functional MRI scanning: No-Conflict (positive-neutral, negative-neutral, neutral-neutral) and Conflict (positive-negative). Crucially, the likelihood of receiving the outcome associated with the objects in each pair was also manipulated (either 100% likelihood of receiving both outcomes or 50% likelihood of receiving one or the other), resulting in 8 possible conditions. Our data revealed that behavioral response and medial temporal lobe activation were driven by conflict as opposed to uncertainty. Moreover, irrespective of uncertainty, AA conflict was associated with greater perirhinal cortex activity. Our findings suggest that involvement of medial

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temporal lobe structures during AA conflict may reflect conflict processing per se, rather than outcome uncertainty.

1-F-207 *Combined and sex-specific volumetric variations observed in adults with alcohol and cannabis use disorders: an ENIGMA-Addiction working group meta-analysis*

Xavier Navarri[1], Mohammad Afzali[1], Patricia Conrod[1]

[1]Université de Montréal

Although numerous studies have compared the volumes of cortical and subcortical regions between SUD participants and controls, the volumetric variations reported through the literature are inconsistent. Meta-analysis methodology could highlight consistent neuroanatomic variations across several studies. The current study investigates the drugs-specific effects of alcohol and cannabis on the adult brain. Based on the ENIGMA-Addiction Group dataset, we performed a volumetric meta-analysis on the cortical thickness and subcortical volumes from six case-control studies (N = 750, 54% are cases) focusing on alcohol use disorder (AUD) and seven case-control cannabis use disorder (CUD) studies (N = 447, 45% are cases). A Cohen's d-effect size estimate was calculated to compare the volumes of the 34 bilateral cortical regions and the seven subcortical regions for each site. Cortical and subcortical volumetric were more affected among AUD participants compared to CUD participants. AUD-participants show reduced volumes in three subcortical and 10 cortical regions whereas CUD-participants have reduced volumes in three cortical regions. Both drugs were associated with reduced volumes in the hippocampus, amygdala and temporal lobe. To highlight sex differences similar analyses were performed for each sex. Male AUD participants showed higher cortical alterations whereas female AUD participants had higher subcortical alterations. None of subcortical regions was affected in either sex with a CUD, however, higher alterations cortical volumes were observed in female CUD participants.

1-F-208 *Ephrins and Eph receptors gene expression regulation and roles in circadian and sleep physiology*

Maria Neus Ballester Roig[1], Lydia Hannou[1], Pierre-Gabriel Roy[1], Erika Bélanger-Nelson[1], Valerie Mongrain[2]

[1]Hôpital du Sacré-Coeur de Montréal, [2]Université de Montréal

Ephrins/Eph are cell adhesion molecules (CAMs) involved in neuron-glia communication and synaptic strength. They are found in the cerebral cortex, hippocampus and the suprachiasmatic nuclei (SCN). EphA4 knockout mice show altered sleep encephalogram and impaired circadian

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responses to light. Also, EphA4 and Ephrin genes contain E-boxes, which suggests gene regulation by clock transcription factors. Thus, we aim to understand if the core clock machinery regulates Ephrin/Eph expression and how this CAM system modulates circadian and sleep variables. We first studied using luciferase assays in COS7 cells if Ephrin/Eph gene expression is regulated by the clock factors CLOCK and BMAL and their homologs, as well as by the clock regulator GSK3β. Secondly, we assessed how in vivo downregulation of this system alters sleep, wheel-running activity rhythm, gene and protein expression. EphA4 was repressed in adult mice by injecting intraperitoneally an EphA4 inhibitor and by the viral-based CRISPR/Cas9 technique to investigate region-dependent effects. Our assays show transcriptional activation of specific promoter regions of EphA4 and EfnB2 by CLOCK-BMAL1 and NPAS2-BMAL1. These effects are repressed when a constitutively active form of GSK3β is co-transfected. In vivo experiments assessing the impact of EphA4 downregulation are in progress and several RNA guides for the CRISPR/Cas9 repression are being tested. Our research will reveal a pathway by which the molecular clock regulates Ephrin/Eph expression, which may influence neurotransmission in a circadian way.

1-F-209 *Altered circadian responses of locomotor activity rhythms in Neuroligin-1 knockout mice*

Maria Neus Ballester Roig[1], Julien Dufort-Gervais[1], Valerie Mongrain[2]

[1]Hôpital du Sacré-Coeur de Montréal, [2]Université de Montréal

Neuroligin-1 (Nlgn1) is a cell adhesion molecule involved in plasticity via regulation of the recruitment of glutamate receptors, presynaptic vesicles and neurotransmitter release. Our previous work showed that the mRNA expression of some Nlgn1 transcripts is rhythmic in the forebrain and that its expression is regulated by clock transcription factors. Therefore, we investigated if Nlgn1 is involved in the regulation of the circadian rhythm of wheel-running activity. To assess circadian activity rhythms and circadian responses to light, Nlgn1-/- (knockout) and Nlgn1+/+ mice were maintained in cages recording wheel-running activity and exposed to different durations of light-dark, dark-dark (DD) and light-light (LL) conditions. The effect of a 1-hour light-pulse was also studied. Finally, brains were sampled after a 1-hour light-pulse to measure molecular changes in the suprachiasmatic nucleus. Our preliminary data reveals that Nlgn1-/- mice have longer periods in DD and increased variability of the time of onset of activity in LL. In the days following a light-pulse, Nlgn1-/- mice showed delayed and more unstable onsets of activity. These findings seems specific to Nlgn1-/- mice since preliminary observations in Nlgn2-/- mice tend to show preserved locomotor activity rhythms. These results demonstrate that Nlgn1 modulates circadian responses to light and suggests that the role of Nlgn1 in synaptic plasticity could be part of molecular pathways underlying circadian physiology.

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1-F-210 *Spontaneous hippocampal neurogenesis is crucial for memory generalization*

Sang-Yoon Ko[1], Sheena Josselyn[1], Paul Frankland[1]

[1]The Hospital for Sick Children/ University of Toronto

Detailed memories become gist-like memories through passage of time, which is referred to as memory generalization. It is believed that the detailed episodic-like memories are initially formed in the hippocampus. In following consolidation period, however, whether hippocampal mechanisms underlying memory transience influence memory generalization has not been fully understood. We note that increasing hippocampal neurogenesis after memory formation promotes reorganization of the hippocampal circuit configuration supporting already stored memory, which in turn facilitates forgetting. It raises a possibility that neurogenesis-mediated forgetting may contribute to decay of detailed hippocampal representation in memory generalization. In this study, we hypothesized that blocking hippocampal neurogenesis after learning prevents memory generalization. To test this idea, we performed irradiation to mouse brain in order to ablate hippocampal neurogenesis. In 3 different hippocampus-dependent memory tests (i.e., contextual fear conditioning, single platform watermaze, and bimodal distribution complex watermaze), neurogenesis-ablated mice showed precise and comparable behavior pattern between short-term (1day) and long-term (28day) delay whereas sham mice showed time-dependent generalizing behavior pattern. Our results suggest that spontaneous hippocampal neurogenesis after memory formation underlies gradual memory generalization.

1-F-211 *Depression and anxiety in PCS patients*

Corinne Doroszkiewicz[1], Charles Tator[1]

[1]University Health Network

Patients diagnosed with a concussion commonly report headaches as well as feeling anxious, and depressed following injury. When symptoms persist, patients are considered to have Postconcussion Syndrome (PCS), which can last for months, years, or indefinitely and affects a considerable percentage of concussion patients. The primary objective of this study is to evaluate the occurrence and management of anxiety and depression in PCS patients and to measure their current quality of life. We sent questionnaires to 528 patients diagnosed with PCS at the Canadian Concussion Centre between 1997 and 2018. The package consisted of a general follow-up questionnaire inquiring about current symptoms, the Depression and Anxiety Stress Scale test (DASS), and the World Health Organization Quality of Life Assessment (WHOQOL-BREF). Completed questionnaire packages were mailed back to us by 105 patients. The DASS and WHOQOL-BREF were scored according to their respective guidelines. Responses were received from 105 patients (20%), 33 (31.4%) of whom scored in the above normal range for depression and 33 (31.4%) of whom scored in the above normal range for anxiety. Of these 33 patients, 25

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patients (23.9%) scored above normal for both anxiety and depression. The average WHOQOL-BREF percentage scores were approximately 10% lower for each of the physical health, psychological well-being, and social relationship domains in comparison to general norms. We are currently in the process of evaluating patient responses pertaining to treatment options for the management of anxiety and depression. Ongoing symptoms of anxiety and depression affect a significant number of PCS patients. In general, PCS patients experience a poorer quality of life as compared to general population norms.

G - Novel methods and technology development

1-G-212 *Predictors of individual variations in corticomotor excitability in response to thermal stimulation*

Yekta Ansari[1], Francois Tremblay[1]

[1]University of Ottawa

The use of thermal stimulation (TS) has been proposed to improve motor function in stroke survivors (Wu et al., 2010). Yet, its neural mechanisms are inadequately understood. Using transcranial magnetic stimulation (TMS), we showed that responses to distal focal cooling produced a variable modulation. Here, we sought to examine potential predictors of thermally-induced variations in corticomotor excitability using markers of sensorimotor integration and intra-cortical inhibition. Participants (n=21, young adults) first underwent TMS. With the index finger wrapped in a gel pack at 24 °C, unconditioned MEPs (n=20) were elicited at 130% motor threshold. Then, blocks of conditioned MEPs were performed to assess short-latency afferent inhibition (SAI), short-latency afferent facilitation (SAF) and short interval intra-cortical inhibition (SICI). Then, MEPs were measured at 1-min with the index finger wrapped in cooled gel pack at ~10°C. Individual responses to cooling varied with about half (11/20) of the participants showing MEP inhibition and the other half showing facilitation (n=7) or no modulation (n=3). Both SAI and SAF proved to be good predictors (r2≥ 0.30) of cooling-induced modulation in corticomotor excitability but not SICI. In particular, high level of SAI was associated with cooling-induced depression, whereas high level of SAF was associated with facilitation. SAI and SAF can be used as markers to predict individual's response to cooling stimulation. This novel finding appears critical to foster any future development of TS as a neurofacilitation method.

1-G-213 *Silicone photomultiplier and lock-in detection for wireless photometry*

Kenneth Loughery[1], Kathryn Simone[1], Kartikeya Murari[1]

[1]University of Calgary

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In vivo photometry is a powerful technique to record from populations of neurons in awake, freely-behaving mice. However, most systems employ an optical fiber tether between a benchtop system and the animal that restricts natural behaviors, and limits testing to primitive environments. Recently, wireless photometry systems have been proposed by others, however the high levels of excitation light required limits the duration of an experiment, due to photobleaching of protein indicators. Towards long-term monitoring in natural environments, we propose a new design of a wireless photometry device. The design is based on a silicon photomultiplier (SiPM) detector, integrated within a coherent detection scheme. The design comprises of the digital implementation of a lock-in amplifier, to minimize weight, with data being transmitted through a Bluetooth Low Energy protocol. Furthermore, miniaturized lenses, filters, and optical fiber cannula are integrated in a 16 mm x 11 mm x 6 mm 3D-printed housing. We present characterization data showing similar performance to a photomultiplier-tube (PMT) based system, suggesting the capacity for translation to in vivo recordings.

1-G-214 *Design of an ultra-fast switching mouse melanopsin variant with a narrow action spectrum*

Raziye Karapinar[1], Dennis Eickelbeck[1], Stefan Tennigkeit[1], Till Rudack[1], Klaus Gerwert[1], Stefan Herlitze[1]

[1]Ruhr-University Bochum

Optogenetics combines the use of light-sensitive proteins and genetical targeting strategies to allow for precise light-controlled manipulation of cell function and signaling in living tissue. We characterized the mouse melanopsin isoform mOpn4L (mus musculus) as a novel optogenetic tool in vivo and in vitro and identified its unique biophysical characteristics and G-protein coupling. Melanopsin functions as a selective molecular light switch for G-protein coupled receptor pathways. We could previously demonstrate that melanopsin is able to sustainably activate and deactivate Gi/o as well as Gq/11 pathways by using short low intensity light pulses for precise activation and deactivation. In the next step we introduced point mutations in mOpn4L to obtain an excitation wavelength shift for future combination with other opsins in tandem activation experiments. Our aim was to create a blue-shifted melanopsin variant maintaining the advantages of mouse melanopsin. Here we show in vitro and in vivo in the cerebellar cortex that the Y211F mouse melanopsin variant, compared to wild type mouse melanopsin, displays a 20 nm blue-shifted absorption maximum combined with faster on and two-fold faster off kinetics while retaining the high light sensitivity of WT melanopsin. Thus, Y211F offers higher temporal precision together with a narrower excitation bandwidth, being an ideal tool to control intracellular G-protein signals with minimal phototoxicity.

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1-G-215 *An open source automated two-bottle choice test apparatus for rats*

Jude Frie[1], Jibran Khokhar[1]

[1]University of Guelph

Two-bottle choice tests are a widely used behavioural paradigm in rodents to determine preference between two liquids, with utility for testing animal models of addiction, depression and anhedonia. Here we describe an open-source 3D-printed, Arduino controlled two-bottle choice apparatus that automatically measures and records drinking behavior in rats to allow for detailed analysis of their drinking microstructure. While commercial products exist that use lickometers, this design uniquely incorporates hydrostatic depth sensors to allow for real-time volumetric measurements in addition to traditional beam-break lick sensing. The goal of this design is to provide an open-source user friendly, affordable apparatus that can study complex behaviours without requiring the purchase of specialized scientific equipment or software. Its applications range from studying alcohol preference in addiction to sugar preference in motivational deficits and reward characterization. This design costs less than $180 CAD to build with decreased costs on each additional device. This design has been successfully tested for accuracy and validated using alcohol preference as an example. The apparatus showed consistency between drinking bouts and volume consumed and is shown to be accurate to 2.7% of the actual volume - an error much smaller than that associated with measuring bottles manually arising from spillage etc. This design makes using the two-bottle choice paradigm more accurate, while also making its data more robust by including both volume and licking incidence.

1-G-216 *In situ validation and spatial mapping of diverse striatal cells identified by scRNA-seq in the mouse brain at single-cell resolution*

Jyoti Phatak[1], Han Lu[1], Hailing Zong[1], Li Wang[1], Li-Chong Wang[1], Morgane Rouault[1], Claudia May[1], David Remedios[1], Jonathan Samson[1], Xiao-Jun Ma[1], Courtney Anderson[1]

[1]Advanced Cell Diagnostics, Inc

Characterizing the transcriptomic profiles of individual cells by single-cell RNA sequencing (scRNA-seq) has become a universal tool to identify novel cell types and understand tissue structure and function. This is especially true in complex organs with high cellular heterogeneity, such as the mammalian brain. However, scRNA-seq results in the loss of spatial organization of cell populations. Validation and spatial mapping of scRNA-seq results can be obtained with assays that retain spatial organization, such as RNA in situ hybridization (ISH). Here we validated and spatially mapped the diverse cell types in the mouse striatum previously identified by scRNA-seq (Gokce et al, Cell Rep, 2016) using the RNAscope multiplex fluorescent ISH assay. We validated the major gene signatures identified, including discrete D1 and D2 medium spiny neuron (MSN) subtypes. Further cellular heterogeneity within the MSN subpopulations was marked by a

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transcriptional gradient, which we spatially resolved with RNA ISH. Lastly, we validated heterogeneity within non-neuronal striatal cell types, including vascular cells, microglia, and oligodendrocytes. These data demonstrate the capabilities of a multiplexed in situ transcriptomic approach for validation and spatial mapping of scRNA-seq results in the highly heterogeneous mouse striatum. Single-cell transcriptomics combined with spatial mapping by RNA ISH holds great promise in resolving heterogeneous tissues at cellular resolution and providing insights into cellular organization and function of diverse cell types in healthy and disease states.

1-G-217 *Interactive user interface for exploring BOLD signal variability-derived functional connectivity*

Daiana Pur[1], Roy Eagleson[1], Sandrine de Ribaupierre[2]

[1]Western University, [2]University of Western Ontario

The brain is inherently a dynamic, massively interconnected structure that is required to undergo fast moment-to-moment switching through network reconfigurations. BOLD signal variability (BOLDSD), a novel index of neural variability derived from functional magnetic resonance imaging (fMRI), supports the emerging view that functional variance supports optimal cognitive performance and enables greater dynamic range of responses to complex stimuli. Despite the increasing interest in this metric and the inherent complexity of fMRI data, there are limited tools for visual representation. We propose a novel user interface implementation to assist in the interactive exploration of BOLDSD connectivity. The tool uses Node.js, a JavaScript runtime built on Chrome's V8 JavaScript engine. An experimental dataset was employed to demonstrate the features of the tool. It consisted of 117 participants, with BOLDSD values obtained at cortical and subcortical brain regions based of Destrieux atlas (n = 168). Correlations between the regions were calculated to obtain connectivity. The user has the option to visualize the connectivity in an interactive matrix form (i.e. choose target and source regions from a drop-down list, with the option to search in search bar), or in an interactive connectome ring format. We show a novel interactive user interface designed to be an exploration tool of BOLDSD variability-derived connectivity. As the number of studies employing BOLDSD is increasing, this tool has the potential to allow neuroscientists to generate new hypotheses and evaluate them.

1-G-218 *Implantable multichannel wireless recording with support for custom electrode configurations for animal electrophysiology*

Jonathan Landes[1], Jessi Mischel[1], Andrew Wilder[1], Brian Crofts[1], Scott Hiatt[1], Daniel McDonnal[1]

[1]Ripple

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Abstract-- We have developed a low-cost inductively powered implantable device for recording multiple independent channels of EMG or LFP data. The recorded data is transmitted wirelessly to an external receiver in real-time. The present design records up to 32 single referenced signals with 12-bit resolution at 2000 samples per second. Exposed solder pins allow for the attachment of custom electrodes through a resealable interface for multi-month animal electrophysiology experiments.

1-G-219 *Deep learning for high-throughput quantification of oligodendrocyte ensheathment at single-cell resolution*

Daryan Chitsaz[1], Yu Kang Xu[2], Robert Brown[2], Qiao Ling Cui[2], Jack Antel[2], Timothy Kennedy[1]

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

High-throughput quantification of myelination by oligodendrocytes is a challenge that, if addressed, would facilitate the development of therapeutics to promote myelin protection and repair. We have established an experimental pipeline in which oligodendrocytes cultured on axon-sized artificial fibers are automatically imaged and analyzed with a deep learning-based algorithm. Oligodendrocytes extend processes along nanofibers and then ensheath them with concentric layers of membrane, recapitulating myelin development in vivo. A convolutional neural network, employing a UNet architecture, was trained to segment and associate ensheathments stained for myelin markers with individual oligodendrocyte cell bodies. The UNet algorithm was able to match the accuracy of expert humans and reliably extract the proportion of ensheathing cells, numbers of sheaths per cell, and multiple morphological descriptors of their ensheathments. The capacity of this technology to perform multi-parametric analyses at the level of individual cells, while reducing manual labor and eliminating human variability, permits the detection of nuanced cellular differences to accelerate the discovery of new insight into oligodendrocyte physiology and pathology. Here, we utilize this highly reduced in vitro assay to investigate the influence of the extracellular protein netrin-1 on oligodendrocytes.

1-G-220 *Clarifying dopaminergic projections of the ventra tegmental area and substantia nigra in humans using structural magnetic resonance imaging*

Nicholas Handfield-Jones[1], Erind Alushaj[1], Nole Hiebert[1], Adrian Owen[1], Ali Khan[1], Penny MacDonald[1]

[1]University of Western Ontario

Substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) dopaminergic (DAergic) projections to the striatum and cortex mediate motor function and a diverse range of cognitive

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behaviours. Accurately measuring these projections in healthy human individuals remains unfulfilled, however. The elucidation of these structural systems would shed light on how the SNc and VTA mediate complex behavioural sequelae in humans. The aim of this study is to a) determine if these projections can be tracked in healthy individuals using ultra-high field magnetic resonance imaging (MRI), and, if so, to b) explore the SNc and the VTA DAergic neural connectivity patterns to striatal and cortical sub-regions. Twenty healthy, elderly participants were scanned in 7-Tesla (7T) MRI. T1-weighted anatomical scans and diffusion weighted imaging (DWI) scans were obtained. The SNc and the VTA were parcellated into limbic, executive, rostral-motor, and caudal-motor sub-regions based on their connections to a striatum parcellation profile previously determined by our lab. White mater probability maps were then generated for each SNc and VTA sub-region using ball-and-stick tractography. Preliminary analysis demonstrates that of all streamlines that emerged from the midbrain, 34.87% and 9.56% targeted the dorsal striatum and the ventral striatum, respectively. In addition, a significant amount also targeted the sub-regions of the cortex, to varying degrees. These data suggest that MRI can track SNc and VTA projections and that these nuclei target a wide range of striatal and cortical sub-regions.

1-G-221 *In vitro optogenetic stimulation using implantable integrated nanophotonic neural probes*

Fu Der Chen[1], Homeira Moradi Chameh[2], Wesley Sacher[3], Ilan Almog[1], Thomas Lordello[1], Xinyu Liu[3], Michael Chang[2], Azadeh Naderian[2], Tianyuan Xue[1], Sara Mahallati[4], Trevor Fowler[3], Eran Segev[3], Laurent Moreaux[3], Michael Roukes[3], Taufik Valiante[5], Joyce Poon

[1]University of Toronto, [2]Krembil Research Institute, [3]California Institute of Technology, [4]IBBME, University of Toronto, [5]Krembil research Institute, University Health Network

Implantable neural probes using passive nanophotonic waveguides and gratings have low heat dissipation and generate controlled illumination patterns that enable optogenetics stimulation with high spatial specificity. We are investigating two types of nanophotonic neural probes based on silicon nitride waveguides: 1) a probe with 16 emission pixels each producing angle-steerable beam patterns, and 2) a probe with 60 emission pixels each emitting a collimated beam. These probes were realized with advanced grating designs and fabricated at a wafer scale on silicon. To investigate the spatial selectivity of optogenetic stimulation, neurophotonic probes were inserted into brain slices of VGAT-ChR2-eYFP mice that were placed on a 60-channel microelectrode array (MEA) with a pitch of 100 um for electrophysiology recording. Hippocampus and cerebellum slices were selected for the experiment due to their high ChR2 expression. For analysis, the spike rate from each MEA channel during light activation was measured and compared to determine the spatial selectivity of optogenetic stimulation enabled by the probes. Both probes are shown to deliver sufficient power to induce robust spike activity across multiple slices. Also, each emission pixel generates a different spike pattern across the MEA. High-resolution beam-steering was

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verified with fluorescent images. This work demonstrates that the nanophotonic neural probes provide spatial selectivity for targeted optogenetics stimulation. Validation of the spatially dependent activity based on a single beam steering pixel is ongoing.

1-G-222 *Fiber-optic tissue identification for electrode placement in deep brain stimulation neurosurgery*

Damon DePaoli[1], Laurent Goetz[1], Dave Gagnon[1], Nicolas Lapointe[1], Gabriel Maranon[1], Léo Cantin[2], Michel Prud'homme[2], Martin Parent[1], Daniel Côté[1]

[1]Université Laval, [2]Hôpital Enfant Jésus

Deep brain stimulation's effectiveness relies on the ability of the stimulating electrode to be properly placed within a specific target area of the brain. Optical guidance techniques that can increase the accuracy of the procedure, without causing any additional harm, are therefore of great interest. We have designed an affordable optical fiber-based device that is small enough to be placed within commercially available DBS stimulating electrodes' hollow cores and that is capable of sensing biological information from the surrounding tissue, using low power white light. With this probe we have shown the ability to distinguish white and grey matter during stereotactic DBS lead implantations on both ex-vivo non-human-primate intact heads, as well as on in-vivo non-human-primates. The in-vivo measurements allowed us to compare simultaneously acquired optical data and neuronal activity using microelectrode recordings. We are in the process of further advancing the procedure using other optical modalities such as spontaneous and coherent Raman spectroscopy - capable of providing molecular composition of the tissue. The addition of these modalities should increase the resolution of our electrode localization and provide the surgeon with regional specificity of the DBS surgical targets (ie. STN and GPI). The end goal will be to deploy this technology during deep brain stimulation neurosurgery in humans, leading to an increase in the accuracy and therefore efficacy of the procedure.

1-G-223 *Machine learning-based seizure prevention with closed-loop brain stimulation*

Gerard O'Leary[1], David Groppe[2], Roman Genov[1], Taufik Valiante[3]

[1]University of Toronto, [2]Krembil Neuroscience Center, [3]Krembil research Institute, University Health Network

A third of these individuals with epilepsy are not successfully treated with current anti-seizure medications (England, 2012). Implanted closed-loop neurostimulation devices can be used to detect the onset of seizures and respond using electrical stimulation to prevent their propagation in the brain. However, existing clinically approved devices have limited efficacy, with only 13% of

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patients achieving seizure freedom for at least a year (Sun, 2014). One challenge involves capturing the complex spectro-temporal seizure dynamics with conventional biomarkers such as changes in physiological signal band energy (SE). However, a recent breakthrough has found a pre-ictal state in the phase locking value (PLV) between brain regions which enables 83% seizure freedom with responsive stimulation in rodents (Salam, 2015). A second challenge involves the patient-specific appearance of seizures due to differences in electrode placement and physiology. To overcome this, data-driven machine learning algorithms can learn patterns in extracted biomarkers such as PLV and SE to accurately classify seizures on a per-patient basis. Our recent work demonstrates the exponentially decaying memory support vector machine (EDM-SVM) algorithm to accurately learn the patient-specific nature of seizures (O'Leary, 2017). An ongoing clinical trial investigates the efficacy of combining SE, PLV and the EDM-SVM with responsive neurostimulation in the reduction of seizures in human epilepsy patients at the Toronto Western Hospital. An early insight into the methods and results are presented here.

1-G-224 *A novel plasma based concussion/traumatic brain injury biomarker for children and adolescents*

Changiz Taghibiglou[1], Sathiya Sekar[1], Hajar Miranzadeh Mahabadi[1], Douglas Fraser[2]

[1]University of Saskatchewan, [2]Western University

Concussion and mTBI are relatively common among children and adolescents mostly due to sport-originated incidences. Concussions in the adolescent patients are of particular concern as their brains are still developing and anatomically are more susceptible to injury. Accurate concussion diagnosis is particularly important for children and adolescents, as it would help in making decisions to stop plays and to provide rapid deployment of treatment and rehabilitation services for the patients. Concussion diagnosis still remains challenging and mostly relays on clinical evaluation of patients as a practicing gold standard. Here we report, plasma ADAM-10 levels as a potential diagnostic biomarker of sport-related concussion in Ontario male adolescent ice hockey athletes (aged 12-14 years). Plasma was obtained from 12 concussed and 17 non-concussed athletes, and analyzed for ADAM-10 levels using ELISA method in a blinded manner. The concussion was confirmed by sport medicine physicians using neurological tests and a Sport Concussion Assessment Tool-3rd edition (SCAT3; 13-14 years of age) or a Child-SCAT3 (for children 12 years of age or younger). The estimated time from concussion occurrence to blood draw at the first clinic visit was 2.3 ± 0.7 days. Plasma ADAM-10 levels were measured at 1855.39±6.76 (mean±SE) and 4039.49±17.97(mean±SE) pg/ml in non-concussed and concussed junior hockey players, respectively (p= 0.01). Our collected data suggests that ADAM-10 may be a potential useful blood-based concussion biomarker.

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1-G-226 ***An innovative approach to evaluating the disease factors in the management of treatment-resistance (TR) for mood disorder in older adults (MDOA)***

Atul Sunny Luthra[1], Theresa Breen[2], Trevor Semplonius[1], Heather Millman[2], Shannon Remers[2]

[1]McMaster University, [2]Homewood Health Centre

An innovative approach has been developed at the Program for Older Adults (POA) at Homewood Health Centre to elucidate the heterogeneity of index episodes and their relevance in TR. Preliminary results from the application of this are being presented as a way of validating the approach. Patients admitted to the POA are evaluated three times a week. The goal is to identify signs & symptoms (S/S) related to the index episode in context of the patient's daily functioning. These are grouped under 4 broad categories: emotional, cognitive, intellectual, & physical. These are subjected to manual factor analysis for each patient at the end of each week in order to establish the phenotypic presentation of the patient's illness. Pharmacological treatment is then tailored to that presentation. This approach is strictly adhered to for the entire duration of their stay. All patients admitted to the POA were administered the 'Residents Assessment Inventory' and the long version of the 'Geriatric Depression Scale' (GDS) at the time of admission and discharge. GDS scores of 20-30 suggest severe depression, 10-19 suggest mild depression, & 9 or less are considered full remission. 107 female and 29 male patients were admitted to the POA between 2012-2015. Average GDS score upon admission was 21.97; average GDS score upon discharge was 8.25. Of 136 patients evaluated, 86 (63.24%) achieved full remission, 42 (30.88%) achieved partial remission, 6 did not show any response, and the final 2 got worse. Over 94% of the patients positively responded to this approach.

H - History, teaching, public awareness and societal impacts in neuroscience

1-H-227 ***Beyond P.I.E.C.E.S. and GPA: 'Meaning' of behaviors in persons with Dementia (PwD)***

Atul Sunny Luthra[1]

[1]McMaster University

There are twelve newly formed behavioral categories to classify behaviors in moderate to advanced Dementia. These categories were used to develop a new behavioral assessment inventory titled LuBAIR (Luthra's Behavioral Assessment and Intervention Response). The reliability and validity of the LuBAIR Inventory was established in an earlier study, where it found that the LuBAIR was less labour intensive, more comprehensive, and offered improved categorization of behaviors into clinically meaningful categories. It was also found that the LuBAIR Inventory has comparable inter- and intra-rater reliability, and Construct and Criteria validity in

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comparison to BEHAV-AD and Cohen-Mansfield Agitation Inventory (CMAI). The advantage of the LuBAIR paradigm lies in its ability to collect more data, and allow data to be put under clinically meaningful categories in order to help understand the 'meaning' of observed behaviors in persons with Dementia. Its use should substantially progress pharmacological and behavioral interventions in Dementia and major neurocognitive disorders (NCD).

IBRO

1-IBRO-228 *SiRNA blocking of mammalian target of rapamycin (mTOR) attenuates pathology in annonacin-induced tauopathy in mice*

Khaled Abbas[1], Mohamed Salama[1], Mahmoud El-Hussiny[1], Wael Mohamed[2], Mohamed Sobh[1], Sabry El-khodery[3]

[1]Mansoura University Faculty of Medicine, [2]Kulliyyah of Medicine, International Islamic University, Kuantan, Pahang, Malaysia, [3]Mansoura University Faculty of veterinary Medicine

Objective: Tauopathy is a pathological hallmark of many neurodegenerative diseases. it is characterized by abnormal aggregates of pathological phosphotau and somatodendritic redistribution. one suggested strategy for treating tauopathy is to stimulate autophagy, hence, getting rid of these pathological protein aggregates. one key controller of autophagy is mTOR. since stimulation of mTOR leads to inhibition of autophagy, inhibitors of mTOR will cause stimulation of autophagy process. the objective of this study was to investigate this hypothesis in a tauopathy model of neurodegeneration. Methods: tauopathy was induced in Twenty-four male c57bl/6 mice using annonacin. Blocking of mTOR was achieved through stereotaxic injection of siRNA against mTOR. The behavioral and immunohistochemical evaluation was done. Results: The behavioral and immunohistochemical evaluation revealed the development of tauopathy model as proven by deterioration of behavioral performance in open field test and significant tau aggregates in annonacin-treated mice. Blocking of mTOR revealed significant clearance of tau aggregates in the injected side; however, tau expression was not affected by mTOR blockage. Conclusions: blocking of mTOR significantly reduced the aggregated tau protein through induction of autophagy and redistribution of aggregated phosphotau rather than through inhibition of tau protein synthesis.

1-IBRO-229 *Behavioral alterations and reduced hippocampal neuroplasticity in an animal model of inhalant abuse*

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Hanaa Malloul[1], Sara Bonzano[2], Mohammed Bennis[1], Giovanna Gambarotta[2], Silvia De Marchis[2], Saadia Ba-M'hamed[1]

[1]University Cadi Ayyad, Faculty of Sciences Semlalia, [2]University of Turin

Thinner is a volatile solvent widely used in various industrial applications and it is a subject to abuse by inhalation for its psychoactive and reinforcing properties. Despite the prevalence of inhalant abuse, the mechanisms underlying the effects of inhalant abuse on the brain are far to be fully understood. In this study, we investigate the consequences of thinner inhalation at behavioral and structural/molecular levels in adult mice following acute (1 day), subchronic (6 weeks) and chronic (12 weeks) exposure to thinner vapor. We found that both subchronic and chronic treatments led to anxiolytic and depressive-like behaviors with altered learning and memory functions, while no changes were observed after acute treatment. Given the well-known implication of adult hippocampal neurogenesis in disease conditions associated with drug abuse, we characterized its alteration following thinner treatments. Notably, prolonged, but not acute thinner inhalation strongly affected adult neurogenesis in the dentate gyrus by reducing progenitor cell proliferation and impairing the survival of newborn neurons. Furthermore, a down-regulation in the expression of BDNF and NMDA receptor subunits as well as a reduction in CREB expression/phosphorylation were found in the hippocampi of chronically treated mice. Our findings demonstrate significant structural and molecular changes in the adult hippocampus following prolonged thinner inhalation, indicating reduced hippocampal neuroplasticity and strongly supporting its implication in the behavioral dysfunctions associated to inhalant abuse.

1-IBRO-230 *5-HT2a receptor in prefrontal cortex participates in the resolution of retroactive interference between object memories during consolidation*

Juan Morici[1], Francisco Gallo[1], Magdalena Miranda[1], Pedro Bekinschtein[1], Noelia Weisstaub[1]

[1]Laboratory of Memory Research and Molecular Cognition, Consejo Nacional de Investigaciones Científic

Historically, memory consolidation was associated with the activity of the medial temporal lobe. However, recently, it was shown that the Prefrontal cortex (PFC) also plays a role, particularly when interfering information is presented. The serotoninergic modulation of PFC has been linked with attentional and executive processes. Though, little is known about the role of this system during the consolidation of interfering memory traces. The object-in-context memory task (OIC) is a recognition protocol in which two object-context associations are generated. Then, depending on the strength of the memory traces, interference between both memories could occurred. Since PFC serotonin type 2a receptor (5-HT2AR) activity has been shown to help prevent memory interference during retrieval, we wanted to evaluate if it participates in the control of memory interference during consolidation. We selectively modulated PFC 5-HT2AR activity after OIC-

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memory acquisition in rats. We observed that activation of 5-HT2AR was required for the resolution of the OIC task only after a weak training that could not be retrieved 24 hs later. Moreover, the PFC 5-HT2AR activity seemed to be required only when two memory consolidation processes were triggered within a specific time window. However, blockade of 5-HT2AR did not affect OIC-memory consolidation when animals generated a long-lasting memory. In summary, our results suggest that the PFC 5-HT2AR activity prevent memory interference in a time and strength dependent way.

Poster cluster: Alzheimer's disease, vascular dysfunction, treatments and cellular plasticity

1-Cluster-231 *A time-course analysis of cell proliferation in the brain following blood-brain barrier modulation using focused ultrasound*

Joseph Silburt[1], Kelly Coultes[2], Kullervo Hynynen[1], Isabelle Aubert[2]

[1]University of Toronto, [2]Sunnybrook Research Institute

Introduction: A diverse range of cells can proliferate in response to blood-brain barrier (BBB) modulation and contribute to regenerative processes in the brain. These cells include microglia, oligodendrocyte precursor cells (OPCs), and neural progenitor cells (NPCs). Transcranial focused ultrasound (FUS) in presence of intravenous microbubbles facilitates a controlled and transient increase in BBB permeability, which is accompanied by a short-term activation of microglia and astrocytes. Previously, we showed that FUS stimulates hippocampal neurogenesis. Here, we provide a time-course analysis on the effect FUS has on microglia, OPC, and NPC proliferation in the hippocampus. Methods: FUS was applied unilaterally to the hippocampus of 3.5 month old C57Bl/6 mice. Mice were sacrificed at 1 day (D), 4D, 7D, 10D. Proliferating cells were labelled with 3 doses of bromodeoxyuridine (BrdU) administered on the day of sacrifice. BrdU-positive cells were detected immunohistochemically. The number of NPCs was quantified as BrdU-positive cells in the sub-granular zone. Proliferating microglia, astrocytes, and OPCs were counted as ki67 cells which co-labelled with Iba1, s100b, and olig2, respectively. Results: Cell proliferation was detected at 1D and 4D post-FUS, and not at 7D and 10D post-FUS. Microglia abundantly proliferate at 1D post-FUS. OPCs and NSCs proliferate maximally at 4D post-FUS. Astrocytes did not proliferate. Conclusion: FUS stimulates tremendous cell proliferation within the first four days, leading to the generation of microglia, OPCs and NPCs in the hippocampus.

1-Cluster-232 *Parameter optimization using Tensorflow in personalized virtual brain models of Parkinson's disease*

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Zheng Wang[1], Kelly Shen[1], Tanya Brown[1], Anthony McIntosh[1]

[1]Baycrest

In large-scale dynamic network modeling efforts, a brute force search on model parameters is often used to optimize the fit between empirical and simulated functional connectivity (FC). However, finding the optimal fit in a brute search is heavily dependent on the choice of search step and space and fitting many parameters at once can become computationally expensive. Here we describe the integration of TensorFlow, a machine learning library with TheVirtualBrain (TVB; thevirtualbrain.org), an open-source software platform for large-scale network modeling. We used data from the Progressive Parkinson's Markers Initiative (PPMI) to create 107personalized models of subjects with Parkinson's disease and healthy controls. Each node was represented by a neural mass model, all coupled together according to the subject's structural connectome. This model can be considered a type of recurrent neural network whose state weights can be trained. Noise (std) served as the input to state weights. State-to-state weights were parameters of interest (i.e., local and global couplings). Fitting was done using the Adam algorithm and we maximized the fit (Pearson r) between simulated and empirical FC. Fitting only two parameters - global coupling and noise - resulted in an average fit of 0.35. By also fitting the interareal couplings (up to 96*96 additional parameters), the fits increased to an average of 0.60. Our findings suggest that integrating machine learning methods into the TVB parameter fitting pipeline can be a powerful tool for large-scale network modeling efforts in the big data era.

1-Cluster-233 *Gene immunotherapy in mouse model of Alzheimer's disease*

Zeinab Noroozian[1], Joseph Silburt[1], Kristiana Xhima[1], Maurice Pasternak[2], Dariush Davani[2], Han Su[3], Kagan Kerman[3], JoAnne McLaurin[2], Sebastian Kügler[4], Kullervo Hynynen[1], Isabelle Aubert[2]

[1]University of Toronto, [2]Sunnybrook Research Institute, [3]University of Toronto Scarborough, [4]University Medicine Göttingen

The efficiency of immunotherapy for Alzheimer's disease (AD) is impeded by the blood-brain barrier (BBB). As such, multiple high doses of antibodies given intravenously are required. We propose a gene immunotherapy approach to facilitate long-term neuronal production of antibodies to efficiently reduce amyloid pathology. We constructed a recombinant antibody against amyloid-beta peptides which was amenable towards packaging into adeno-associated virus (AAV), and validated for target binding in a mouse model of AD. We evaluated our anti-amyloid recombinant antibody for expression, secretion, binding affinity, and impact on cell survival in vitro. We confirmed the high binding affinity of the recombinant antibody to soluble monomer and oligomer amyloid-beta peptides. We then, transferred our gene construct into an AAV vector and delivered to the mouse brain intracranially, or through intravenous administration combined with MRI-guided focused ultrasound to locally and temporarily increase BBB permeability. We assessed the

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expression of the transgene and efficacy in reducing amyloid plaque pathology in the brain. Neurons were found capable of expressing and secreting the transgene in vitro and in vivo. Long-term in vivo expression of the therapeutic was detected up to 14 months. A significant reduction in amyloid-beta plaques was detected at the site of transfection at 3-7 months post-delivery. A single gene therapy treatment leading to the sustained production of an anti-amyloid recombinant antibody can provide long-term efficacy in reducing AD-related pathology.

1-Cluster-234 *Blood-brain barrier modulation in the basal forebrain with focused ultrasound enhances delivery of a nerve growth factor mimetic in a mouse model of Alzheimer's disease*

Kristiana Xhima[1], Kelly Markham-Coultes[2], Hinyu Nedev[3], H. Uri Saragovi[3], Kullervo Hynynen[1], Isabelle Aubert[2]

[1]University of Toronto, [2]Sunnybrook Research Institute, [3]McGill University

Dysfunction and loss of basal forebrain cholinergic neurons (BFCNs) are associated with cognitive impairment in Alzheimer's disease (AD). The disruption of nerve growth factor (NGF) signaling, which enables cell survival and neurite growth-enhancing signals, contributes to BFCN degeneration. Thus, restoring NGF signaling in BFCNs may lead to effective therapies for cholinergic deficits in AD. To date, clinical translation of NGF-based therapeutics have been limited by poor pharmacological stability, undesirable pleiotropic effects by binding of p75 receptor in the absence of tropomyosin receptor kinase A (TrkA), and lack of penetration across the blood-brain barrier (BBB). In this proof-of-concept study, we report a novel therapeutic approach designed to resolve the limitation posed by the BBB in the delivery of NGF-based strategies for AD. We demonstrate noninvasive and targeted delivery of a non-BBB permeable, high-affinity agonist of TrkA with favourable pharmacological properties to BFCNs using MRI-guided focused ultrasound (MRIgFUS) in the TgCRND8 mouse model of AD. MRIgFUS allows for a transient and localized increase in BBB permeability in selected brain areas. Intravenously injected TrkA agonist was delivered to MRIgFUS-targeted regions. TrkA phosphorylation and activation of downstream signaling cascades, including MAPK, Akt and CREB were enhanced following treatment. This study highlights the feasibility of TrkA activation using a selective agonist delivered by MRIgFUS to BFCNs, stimulating survival and plasticity signaling pathways in a mouse model of AD.

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1-Cluster-235 *A developmentally-induced cell stress response in TSC2-/- NSCs drives brain-specific disease phenotypes and therapeutic vulnerabilities in Tuberous Sclerosis Complex*

Lisa Julian[1], Sean Delaney[1], Carole Dore[1], Julian Yockell-Lelievre[1], Adam Pietrobon[1], William Stanford[1]

[1]Ottawa Hospital Research Institute

We have engineered the first human pluripotent stem cell (PSC) model of Tuberous Sclerosis Complex (TSC) that recapitulates multiple neural and mesenchymal cell types of this devastating neurocognitive and tumor disorder. TSC2-/- PSCs (2 male, 2 female lines) established through CRISPR-Cas9 genome editing are mTORC1 hyper-active and rapidly adopt multi-lineage disease phenotypes upon differentiation into neural stem cells (NSCs) and neural crest cells (NCCs). RNA-seq and functional analysis during lineage development revealed activation of an endoplasmic reticulum stress response in neuralized TSC2-/- cells. This is resolved in NCCs but persists in TSC2-/- NSCs, and underlies long-term up-regulation of mitochondria and lysosome biogenesis, autophagic flux, protein aggregates, and glycolytic and oxidative metabolism in TSC2-/- neural cells. These phenotypes model TSC cortical tubers and epilepsy, yet are counter-intuitive to the current understanding of mTORC1 signaling; critically, we show they are rapamycin-independent and driven by activation of atypical NSC-specific pathways, including ULK1 phosphorylation by AMPK to drive autophagy. Strikingly, this chronic stress response selectively sensitizes TSC2-/- NSCs, but not NCCs, to death with autophagy and proteasome inhibitors. Our findings reveal a critical mechanism by which TSC2 regulates brain development, highlights the power of PSC modeling to unveil disease mechanisms and vulnerabilities in the relevant cell lineages, and offers novel therapeutic insight for TSC and other neurological diseases impacted by TSC-mTOR.

1-Cluster-236 *BrainReach/Mission Cerveau: An innovative way to bring neuroscience to the community*

Eviatar Fields[1], Marie-Julie Allard[2], Samuel Guay[2]

[1]McGill University, [2]on behalf of BrainReach/Mission Cerveau at McGill University

BrainReach/Mission Cerveau is a non-profit, bilingual community outreach program designed to promote science education in under-resourced elementary schools, highschools and penitentiaries around Montreal, Quebec. Through interactive and engaging neuroscience-based workshops, we teach students about brain function, remove the stigma around mental illnesses, and increase the understanding of what it is to be a scientist. Moreover, our sister organization BrainReach North/Mission Cerveau Nord develops remotely accessible lesson content and sends volunteers on teaching outreach trips to indigenous communities and remote regions of Northern

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Quebec. BrainReach/Mission Cerveau is just the beginning of what we hope will become an established supplement to science teaching.

1-Cluster-237 *Misoprostol alters the migration and differentiation of neuroectodermal stem cells*

Denis Adigamov[1], Dorota Crawford[1]

[1]York University

Misoprostol (MP) is a prostaglandin type E analogue associated with neurodevelopmental disorders such as Moebius syndrome and Autism Spectrum Disorders (ASD). MP acts on the same E-Prostanoid receptors (EP 1-4) as the major lipid mediator in the developing brain called prostaglandin E2 (PGE2). Our previous studies showed that increased level of PGE2 affected the migration, rate of differentiation, and expression of ASD linked genes in neuroectodermal (NE4C) stem cells. The goal of this study was to determine whether MP can also alter the behaviour of undifferentiated and differentiating NE4C cells. Through time-lapse microscopy, we determined that MP exposure caused an approximately 25% reduction in the speed and distance travelled by NE4C stem cells. Moreover, MP delayed the differentiation of NE4C cells, apparent by the delayed expression of MapT differentiation marker and retained expression of Oct4 stem cell marker. Furthermore, during the differentiation period, MP exposure led to the formation of larger neuronal clusters (neurospheres) when compared to the control. This was associated with increased expression of Cdh2 adhesion molecule, which has been important for neuronal migration, signalling and differentiation. We conclude that MP can influence the migration of neuronal stem cells and progression of neuronal differentiation. These findings add to our previous studies which suggest that exposure to MP at critical periods in development may result in neuronal pathology.

1-Cluster-238 *Prostaglandin E2 affects the expression of neuronal hemoglobin- link to autism spectrum disorders*

Isabel Bestard-Lorigados[1], Ravneet Rai-Bhogal[1], Christine Wong[1], Dorota Crawford[1]

[1]York University

Hemoglobin isoforms are usually found in erythrocytes as a tetramer of alpha (Hba-α) with gamma (Hbb-γ) chains during fetal stages, and alpha with beta (Hbb-β) in postnatal stages. Although hemoglobin was recently found to be expressed in neuronal cells, the function and heteromerization of the isoforms in the brain are unclear. Previous microarray analysis detected abnormal levels of Hbb-β and Hbb-γ in the prenatal male brain of our autism mouse model lacking prostaglandin E2 (PGE2) producing enzyme cyclooxygenase-2 (COX2-/-). The COX-2/PGE2

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pathway is involved in healthy neurodevelopment and its abnormal signaling has been linked to Autism Spectrum Disorders (ASD). In this study, we use quantitative Real-Time PCR and Western Blots to investigate the expression of Hba-α, Hbb-γ and Hbb-β in the brain of the COX2-/- male and female mice at postnatal day 25. Gene expression of fetal Hbb-γ in postnatal brains of COX2-/- mice was higher in females compared to males (by 1.9 fold), whereas no sex-difference was found for wild-types. Hbb-γ levels were significantly upregulated in the COX2-/- females (by 7.6 fold) and COX2-/- males (by 7.8 fold) compared to the respective wild-type. Gene levels of Hba-α and Hbb-β were not affected in COX2-/- mouse. Interestingly, Hbb-γ and Hbb-β proteins formed dimers and tetramers in the postnatal brain. These initial results add new knowledge about the expression of hemoglobin isoforms in the postnatal brain as well as the involvement of COX-2/PGE2 pathway in regulation of neuronal hemoglobin expression with potential implications to ASD.

1-Cluster-239 *Microglia activity in the mouse brain lacking prostaglandin E2 producing enzyme cyclooxygenase 2- connection to autism*

Sarah Wheeler[1], Ravneet Rai-Bhogal[1], Dorota Crawford[1]

[1]York University

Prostaglandin E2 (PGE2) is a signaling molecule produced by cyclooxygenase-2 (COX-2) and is important in normal brain development and in microglia activation during inflammation. Anomalies in the COX-2/PGE2 pathway due to genetic or environmental factors have been linked to Autism Spectrum Disorders (ASD). Our previous studies found that the COX2-/- mouse is a good model system for studying the link between COX-2/PGE2 and ASD. Here, we examined the effect of abnormal PGE2 signaling on microglia activation in postnatal mice brains lacking COX-2 enzyme (COX2-/-). Using immunohistochemistry for microglial marker Iab-1 we quantified sex-dependent microglial density, activation state and branch length in the COX2-/- offspring compared to the respective wild-type (WT) controls at postnatal day 25. Microglial density was significantly increased in the COX2-/- female hippocampus compared to the WT female. The number of active microglia decreased in COX2-/- males in the thalamus, but increased in COX2-/- females in the hippocampus compared to the respective WT. The number of resting microglia was also higher in COX2-/- males within the cerebellum and the prefrontal cortex compared to WT males. Average branching length in the resting microglia, suggesting a prolonged resting state, was increased in COX2-/- males within the thalamus and COX2-/- females in the hippocampus. These results indicate that abnormal COX-2/PGE2 signaling can affect microglial activation and duration of the resting state in the brain, in a sex-dependent manner, which can potentially lead to brain pathology.

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1-Cluster-240 *Prenatal exposure to Prostaglandin E2 leads to abnormal cell density and migration in the mouse brain - link to Autism*

Christine Wong[1], Isabel Bestard Lorigados[1], Dorota Crawford[1]

[1]York University

The prostaglandin E2 (PGE2) pathway is important for neurodevelopmental processes such as neuronal proliferation and migration. Abnormal levels of PGE2 can result from various environmental or genetic risk factors and have been linked to Autism Spectrum Disorders (ASD). Our previous studies in mice revealed that a single maternal injection of PGE2 during pregnancy at gestational day 11 (G11) affects expression of various ASD genes and leads to sex-dependent autism-related behaviours in offspring. In this study, we used CldU and IdU labelling to investigate whether maternal PGE2 exposure at G11 also effects proliferation and migration of cells originating at G11 or G16. We quantified cell density in the cerebellum, hippocampus, olfactory bulb, and neocortex, as well as cortical cell migration at postnatal day 8. PGE2-exposed mice had lower cell densities in the cerebellum and neocortex but the opposite effect was observed in the olfactory bulb. Neocortical cell density differences were specific to PGE2-exposed females, while differences in the olfactory bulb were only detected in PGE2-exposed males. Cortical cells also migrated a greater distance in PGE2-exposed mice. The expression of cell growth and motility genes, beta-actin (Actb) and spinophilin (Spn), were also decreased in PGE2-exposed males but increased in PGE2-exposed females. These findings together with our previous molecular and behavioural data strengthen the knowledge that alterations in PGE2 levels during critical prenatal periods can affect normal brain development and contribute to ASD pathogenesis.

1-B-241 *Deep learning-based analysis of optical nanoscopy images reveals activity-dependent reorganization of the periodical actin lattice in dendrites*

Flavie Lavoie-Cardinal[1], Anthony Bilodeau[1], Mado Lemieux[2], Marc-André Gardner[2], Theresa Wiesner[1], Gabrielle Laramée[1], Christian Gagné[1], Paul De Koninck[2]

[1]CERVO Brain Research Center, [2]Université Laval

The discovery of the actin-spectrin membrane-associated lattice using super-resolution optical microscopy changed our understanding of the organization of actin, a key protein of the neuronal cytoskeleton. This lattice, containing actin rings periodically spaced 180 nm apart, was initially discovered in axons and later observed in dendrites of multiple of neurons. However, its role and regulation mechanisms remain unknown. We demonstrate that neuronal activity regulates the actin-based lattice in dendrites but not in axons of cultured rat hippocampal neurons. Using STimulated Emission Depletion (STED) nanoscopy, we observed complex and diverse patterns

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of fluorescently-labelled F-actin inside neuronal processes. While the F-actin periodical ring patterns were robustly detectable in axons, dendrites exhibited patches of actin rings perpendicular to the shaft, mixed with patches of longitudinal fibers parallel to the shaft axis. This diversity of patterns posed a colossal challenge for quantitative analysis, which we addressed using a deep learning segmentation approach. We trained a fully convolutional neural network to identify the periodical actin lattice and longitudinal actin fibers in STED images of fixed neurons. With this approach we could quantify the extent of the periodical lattice and the fibers on a large dataset and at various neuronal activity levels. We observed that increasing neuronal activity leads to the reorganization of the periodical lattice in dendrites but that it remains stable in axons.

1-A-242 *Effects of elevated prenatal testosterone and prenatal dexamethasone on hormone profiles and stress responsivity in mice*

Hayley Wilson[1], Emily Martin[1], Elena Choleris[1], Neil MacLusky[1]

[1]University of Guelph

Sex steroid hormones, such as testosterone (T), program the brain during sensitive periods of development, resulting in sexual differentiation of neuroendocrine function and behaviour. Slight elevations in prenatal T have been hypothesized as a risk factor for Autism Spectrum Disorder, a developmental disorder which predominantly affects males. The underlying mechanisms remain unknown. Prenatal T and glucocorticoid (GC) exposure have been reported to have similar effects on offspring behaviour. Thus, we hypothesized that prenatal low dose T and GC exposure might interact and exert similar effects on the developing brain. Prenatal GC exposure can disrupt sex steroid levels and stress responsivity in offspring. We assessed the impact of elevated prenatal testosterone and dexamethasone (DEX; a synthetic GC) on hormone profiles and GC levels in mice. Pregnant CD1 mice were treated with T propionate (10ìg), DEX (50ìg/kg), or sesame oil on gestational days 12, 14, and 16. T was measured in male pups from 1 to 6 hours after birth. Corticosterone (CORT) was measured during adolescence in hair samples, as well as in adulthood in plasma at 10 minutes, 1 hour, or 3 hours following 30-minute restraint stress. Neither prenatal T or DEX affected T levels in male pups. While prenatal T had no effect on CORT levels in hair, prenatal T reduced CORT responsivity to restraint stress in males, but not in females. No effects of prenatal DEX on adult CORT responsivity were observed, in either sex. Thus, low doses of prenatal T alter stress responsivity in males, consistent with the hypothesis that prenatal increases in T levels may selectively impair development of the male hypothalamic-pituitary-adrenal axis.

1-Cluster-243 *Focused ultrasound mediated IVIg immunotherapy in the hippocampus enhances the proliferation of neural progenitor cells in a mouse model of amyloidosis*

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Sonam Dubey[1], Maurice Pasternak[1], JoAnne McLaurin[1], Donald Branch[2], Kullervo Hynynen[3], Isabelle Aubert[1]

[1]Sunnybrook Research Institute, [2]Canadian Blood Services, [3]University of Toronto

Intravenous immunoglobulin (IVIg) contains natural antibodies collected from thousands of healthy blood donors that have been shown to increase neurogenesis in multiple mouse models. Previously, we evaluated the effect of two treatments of IVIg delivered to the hippocampus with focused ultrasound (FUS) and found that IVIg-FUS therapy increased neurogenesis by 3-fold compared to IVIg-alone. We questioned whether a second treatment would further increase the proliferative capacity of cells after the first treatment. To answer this question, we used a mouse model of amyloidosis to evaluate hippocampal proliferation when given 0.4g/kg IVIg intravenously, with or without the application of FUS. Two spots of FUS were applied unilaterally to the left hippocampus, while the contralateral side served as a control for IVIg without FUS. Tissue collection occurred at day 3, 10 and 21 to delineate the effects of two treatments (day 1 and 8). We performed a cell lineage tracing study using bromodeoxyuridine and ethynyldeoxyuridine as the proliferative immunohistological markers after each treatment. We found that both FUS-alone and IVIg-FUS therapy increased the proliferation of cells after two treatments. However, with the second treatment, only IVIg-FUS therapy increased the survival of neuroblasts without detrimentally affecting the cells proliferated after the first treatment. Our results show that a repeat IVIg-FUS therapy is safe for clinical translation as it enhances the proliferative capacity of neural progenitor cells with the additional treatment.

1-Cluster-244 *Cerebrovascular dysfunction in a mouse model of Alzheimer's disease*

Madelaine Lynch[1], Lynsie A.M. Thomason[1], Rafal Janik[1], Illsung Lewis Joo[1], Bojana Stefanovic[1], Isabelle Aubert[1]

[1]Sunnybrook Research Institute

Cerebrovascular dysfunction is being recognized in patients with Alzheimer's disease (AD). Compromise of the cerebrovasculature manifests as reduced cerebral blood flow, impairing delivery of oxygen and nutrients, leading to poor neuronal function in the brain. The TgCRND8 mouse model of AD has been demonstrated to have a blunted response to hypercapnia induced vasodilation, as evidenced by an elongated transit time (Dorr, 2012). As such, we sought to further characterize this dysfunction using blood oxygenation level dependent (BOLD) and arterial spin labeling (ASL) functional MRI. Functional MRI data was acquired from transgenic (Tg) and non-Tg mice, aged 7.5 months. In the hippocampus we detected a significant attenuation of the BOLD and ASL responses to hypercapnia (5% CO2, 65% oxygen, 30% nitrogen) in Tg with respect to non-Tg mice. There were no significant differences in cortical responses to hypercapnia. To elucidate the molecular mechanisms underlying the blunted hypercapnic response, we used a

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separate cohort of mice for biochemical and histochemical analyses. As the response to hypercapnia is largely mediated by arachadonic acid (AA) metabolism, we analyzed a number of downstream mediators of AA signaling. This is the first study to demonstrate hippocampal vascular reactivity in TgCRND8 mice using fMRI, while further providing insight into the molecular mechanisms underlying cerebrovascular dysfunction in AD.

Poster session 2: May 24, 2019

A - Development

2-A-1 *Mechanisms controlling neural stem cell quiescence*

Danielle Jeong[1], Archana Gengatharan[2], Armen Saghatelyan[3], David Kaplan[4], Freda Miller[4], Scott Yuzwa[1]

[1]University of Toronto, [2]Centre de Recherche de l'Institut Universitaire en Santé Metale de Québec, [3]Université Laval, [4]The Hospital for Sick Children

Adult neural stem cells (NSCs) in the ventricular-subventricular zone (V-SVZ) are relatively quiescent in nature, dividing infrequently to ensure a lifelong supply of new olfactory bulb neurons but primed to activation upon brain injury. NSCs derive from developing forebrain radial precursors (RPs) during late embryogenesis, when they transition from a rapidly-proliferative to a relatively quiescent 'slow-dividing' state. Mechanisms underlying this transition, however, are still unclear. Recently, we have captured the RP to NSC transition using high-throughput single-cell RNA-sequencing (scRNA-seq) collected from the embryonic cortex (Yuzwa et al., Cell Reports, 2017). We showed that RPs and NSCs are transcriptionally similar, suggesting that the transition to the slow-dividing state may be controlled extrinsically. To investigate the extrinsic mechanism, we exploited our scRNA-seq data to identify cell-surface proteins that control quiescence in other cell types. We found that a negative regulator of receptor tyrosine kinases, leucine-rich repeats and immunoglobulin-like domain 1 (LRIG1), is enriched in emerging slow-dividing RPs. Knockdown of Lrig1 in RPs in culture or in vivo inhibited transition to the slow-dividing state. Lrig1 expression was maintained in NSCs postnatally and targeted Lrig1 disruption in the postnatal V-SVZ with CRISPR/Cas9 robustly increased NSC proliferation. Collectively, these data identify LRIG1 as a key regulator of NSC quiescence, likely by preventing growth factor receptors from responding to extrinsic proliferative cues within the NSC niche.

2-A-2 *The proteomic architecture of human fetal neural progenitor cells*

Jennifer Kao[1], Ugljesa Djuric[2], Mike Papioannou[2], Ihor Batruch[3], Patrick Shannon[3], Phedias Diamandis[1]

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[1]University of Toronto, [2]University Health Network, [3]Mount Sinai Hospital

During fetal neurogenesis, proper maturation of neural progenitor cells to cortical GABAergic inhibitory interneurons is necessary for normal regulation of excitatory neuron activity and the establishment of mature neuronal circuits. Examining the molecular profiles of progenitor compartments from which these interneurons arise is critical for understanding interneuron maturation. We have conducted a spatial proteomic profile of formalin-fixed, paraffin-embedded human fetal brain regions (n=8) implicated in interneurogenesis (dorsal subventricular zone (DSVZ), medial and lateral ganglionic eminences (MGE, LGE), neocortex, subplate, striatum). Using a label-free mass spectrometric method, we quantified >2100 proteins and identified region-specific proteins which may play a functional role in GABAergic interneuron maturation. Well-established proteins such as SATB2 and DBN1 in the cortex or NES in the progenitor compartments were found to be significantly upregulated (FDR<0.05) while unsupervised analysis reveals multiple protein clusters with distinct, region-specific expression profiles. Immunofluorescent stains of candidate neocortex- and MGE-specific biomarkers were similarly positive in CTIP2+ and SOX2+ cells, respectively. Functional validation assays of these candidates in cerebral organoid culture present with distinct phenotypes, including stunted growth and excessive neuroepithelial budding. Ultimately, this data provides insight into previously uncharacterized proteins and their potential, significant role during cortical interneuron development.

2-A-3 *The role of endocannabinoid signaling during spinal cord regeneration in Ambystoma mexicanum*

Michael Tolentino[1], Gaynor Spencer[1], Robert Carlone[1]

[1]Brock University

Research into the molecular mechanisms of the psychoactive effects of cannabis has led to the discovery of the endocannabinoid system (ECS), a neuromodulatory system conserved in many organisms. Although evidence for its modulatory role in normal CNS development is increasing, far fewer studies have focused on its function in response to trauma in the CNS in mammals. Moreover, nothing is known regarding the role of endocannabinoid in CNS regeneration-competent species like the Mexican axolotl, one of the few vertebrates than can regenerate their spinal cord. We provide preliminary evidence that suggests that expression of the CB1 protein (the main EC receptor in the CNS) is altered in the caudal spinal cord and tail tissues in response to amputation. In addition, in vivo disruption of CB1 signalling with the treatment of the selective antagonist/reverse agonist, AM251, significantly inhibited caudal growth of the spinal cord and tail by 10 days post amputation. Immunofluorescent analyses to identify the tissue and cellular distribution of CB1 during normal caudal spinal cord regeneration and after inhibition with AM251 are presently underway. We will also assess the effects of CB1 inhibition on proliferation and

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differentiation of GFAP+ ependymoglial cells. This study is the first to determine the role of the ECS during spinal cord regeneration in a regeneration-competent vertebrate model and may aid developing novel therapies for human nervous system injuries or pathologies.

2-A-4 *Effects of early-life stress on AMPA receptors in the auditory cortex*

Carinna Moyes[1], Aycheh Al-Chami[1], Hongyu Sun[1]

[1]Carleton University

Critical period (CP) plasticity in the auditory cortex (A1) has been known to be crucial for both functional brain development and cognitive function. Impaired A1 development during a CP for tonotopic mapping has been implicated in many neurological disorders of learning and memory, including Autism. Our recent results have shown a critical role for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) in the auditory CP for tonotopic mapping. Here, we aim to determine if early-life stress (ELS) during rapid synaptic development affects the function of AMPARs required for normal CP plasticity. ELS was induced at P3-11 in a c-Fos based transgenic mouse model. Using whole-cell patch-clamp recordings, we recorded pyramidal cells in layer IV of A1 to measure AMPAR function and the maturation of glutamatergic synapses in P12-15 mice. We found that AMPAR functional maturation is highly correlated to the opening of A1 tonotopic CP plasticity during normal development. We further identified that ELS selectively activated a subpopulation of A1 pyramidal neurons as evidenced by selective activity-dependent green fluorescent protein (GFP) tagging. Interestingly, while ELS did not cause significant changes in AMPAR function in overall randomly sampled neurons, ELS activated neurons showed enhancement of AMPAR function compared to non-activated neurons. These results provide a potential synaptic mechanism following exposure to a stressor during a CP of brain development and might identify novel strategies to modulate ELS-induced neurodevelopmental impacts.

2-A-5 *npat regulates the retinal progenitor cell population and replication dependent histone transcript synthesis in postembryonic zebrafish*

Monica Dixon[1], Michael Mattocks[1], Maria Sartori[1], Jason Willer[2], Ronald Gregg[2], Vince Tropepe[1]

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

We present an in vivo study of npat function in larval zebrafish. npat has been shown to be required for the formation of histone locus bodies and transcription of replication dependent (RD) histone genes in human cells and in Drosophila. We characterized the cellular phenotype of the zebrafish mutant rys, showing that the retinal ciliary marginal zone (CMZ) progenitor cell population has

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abnormalities in cell cycling, differentiation and survival. We mapped the rys mutation to the npat gene, finding that it removes a splice donor, leading to intron retention. The resulting predicted premature stop codon would cause the loss of the C-terminal 80% of the NPAT protein, including nuclear localization signals and phosphorylation sites required for RD histone transcription. Surprisingly, we observed elevated levels of total RD histone transcripts in the rys mutant, in contrast to the decrease others have seen in human cells and in Drosophila. The elevation in zebrafish was even more pronounced for poly-adenylated RD histone transcripts, consistent with a role for zebrafish NPAT in 3' end processing of RD histone transcripts to generate their characteristic 3' stem loop rather than the polyA tail, which is normally added to other mRNAs. This agrees with others' suggestion that NPAT in human cells may have such a histone mRNA 3' end-processing role. Our future experiments will explore the mechanism(s) by which NPAT regulates RD histone transcript synthesis in zebrafish and the link between RD histones and CMZ progenitor cell behaviour.

2-A-6 *The elucidation of neuronal cell fate specification from cortical neural stem cells using single cell transcriptional profiling*

Michael Borrett[1], Mekayla Storer[2], David Kaplan[2], Freda Miller[2]

[1]University of Toronto, [2]The Hospital for Sick Children

Radial precursors (RPs) produce the major cell types of the cerebral cortex and establish a population of adult neural stem cells (NSCs) that resides in the mature brain. Embryonic RPs and their adult NSC progeny are functionally different from one another: embryonic cortical RPs produce excitatory glutamatergic neurons that populate the cortex whereas cortically derived adult NSCs produce inhibitory GABAergic neurons that migrate to the olfactory bulb. The timepoint at which cortical RPs switch from making excitatory to inhibitory neurons and the mechanism by which this switch occurs remain poorly understood. Here, we have employed a microfluidic single cell transcriptomic technology coupled with transgenic lineage tracing in order to molecularly profile cortically derived NSCs and their progeny during embryonic and postnatal development. Our findings indicate that cortically derived NSCs almost exclusively produce inhibitory neurons as early as two days after birth. We have subsequently identified an embryonic population of cortically derived immature plastic neurons that express genes characteristic of both excitatory and inhibitory neurons, suggesting that they are not yet committed to one versus the other fate. Together our findings suggest that cortically derived NSCs may in fact not intrinsically "switch" from making excitatory to inhibitory neurons but rather are multipotent in generating either excitatory or inhibitory neurons both in the embryonic and postnatal brain and it is their environment that ultimately dictates their cell fate specification.

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2-A-7 *Ehmt1/GLP protein expression is enhanced in newborn and migrating cells of neurogenesis areas in mouse and rat brain*

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

[1]Radboudumc

Euchromatin histone methyltransferase 1 (Ehmt1) is a protein which regulates transcription by catalyzing methylation of histones, leading 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). 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 adult brain and demonstrated that in all cells in all parts of mouse and rat brain the Ehmt1 protein is localized, by measuring the nuclear Ehmt1 immunostaining density in many individual cells in many different brain areas. Interestingly, significantly elevated levels were found in the two known adult rodent neurogenesis areas: the Dentate Gyrus Subgranular layer (DG/SGL) and the subventricular zone-RMS-Olfactory bulb areas. The number of darkly stained Ehmt1-positive cells appears to be similar to the number of DCX-positive cells in DG/SGL, indicating the importance of Ehmt1 in adult neurogenesis.

2-A-8 *Changes in microRNA localization during growth cone guidance*

Sarah Walker[1], Robert Carlone[1], Gaynor Spencer[1]

[1]Brock University

During axon path-finding, neuronal growth cones navigate towards their synaptic target with extreme accuracy and precision. The growth cone rapidly responds to various external guidance cues, including classical chemotactic proteins such as netrins and semaphorins. Recent studies have identified a variety of non-traditional guidance cues, including the Vitamin A metabolite, retinoic acid (RA), which can act as a chemoattractant during growth cone guidance. However, little is known regarding the underlying molecular mechanisms regulating RA's effects in this context. MicroRNAs, a class of conserved non-coding RNA transcripts, have emerged as important components in regulating growth cone guidance through local protein synthesis. Studies exploring the role of microRNAs in growth cone guidance are limited, and mostly examine microRNA expression in response to classical guidance cues. Our goal is to identify microRNAs that regulate growth cone guidance in response to a non-traditional guidance cue, RA. We have previously shown that growth cones of isolated molluscan motor neurons turn towards RA in a local protein synthesis-dependent manner, and that miR-124 is expressed in cells that respond to

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RA. However, we now show that the subcellular distribution of this microRNA changes during RA-induced growth cone turning responses. These studies will advance our knowledge of growth cone dynamics and local protein synthesis, with particular emphasis on the underlying mechanisms of RA-induced chemoattraction.

2-A-9 *A gradient of netrin-1 directs commissural axon extension in the embryonic spinal cord*

Celina Cheung[1], Karen Lai Wing Sun[1], Stephanie Harris[1], Reesha Raja[1], Daryan Chitsaz[1], Jean-Francois Cloutier[1], Timothy Kennedy[1]

[1]McGill University

Gradients of secreted long-range attractant and repellent proteins have been proposed to guide growing axons to their targets during development. Netrin-1, a major midline cue that is essential for commissural axon guidance in the embryonic spinal cord, is expressed by cells in the ventricular zone and floor plate. Studies in embryonic mouse spinal cord and hindbrain have shown that netrin-1 expressed by ventricular zone progenitor cells is necessary for commissural axons to reach the midline, and that selective deletion of netrin-1 from the floor plate alters commissural axon trajectories as they approach the ventral midline. Netrin-1 expression is essential for commissural axon extension; however, it remains unclear to what extent netrin-1 proteins functions as a long-range attractant that directs axon growth. We address how the distribution of netrin-1 protein influences axon guidance in the developing spinal cord. In early embryonic chick spinal cord, netrin-1 is expressed only by floor plate cells, yet we detect netrin-1 protein in a gradient that extends 100-200µm dorsal of the floor plate. In the embryonic mouse spinal cord, our findings indicate that secretion by floor plate cells with ventricular zone expression produces a similarly graded distribution of netrin-1 protein. In functional assays, we demonstrate that manipulating the distribution of netrin-1 in the embryonic spinal cord redirects commissural axon extension. These findings indicate that the precise distribution of netrin-1 protein directs commissural axon extension in the embryonic spinal cord.

2-A-10 *Effects of Val66Met BDNF polymorphism on cortical GABAergic circuit refinement*

pegah chehrazi[1], Graziella Di Cristo[1]

[1]Université de Montréal

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Parvalbumin (PV)-expressing GABAergic interneurons constitute the majority of interneurons in the cortex and strongly regulate principal cell output and plasticity. One of the strongest modulators of PV network development and experience-dependent plasticity is Brain-Derived Neurotrophic-Factor (BDNF). BDNF is first synthesized as a precursor (proBDNF) which is cleaved to generate mature BDNF (mBDNF) and the prodomain (pBDNF). We have previously shown that proBDNF induces PV cell synapse pruning. Emerging data suggest that a common single-nucleotide polymorphism (SNP) in pBDNF, i.e. methionine (Met) substituting for valine (Val) at codon 66 (Val66Met), is associated with genetic predisposition to anxiety and depression. Here, we investigated whether and how different pBDNF SNPs affect cortical PV interneuron axon morphology and synapse development. We labeled isolated PV interneurons and their axons, by driving GFP expression with a previously characterized promoter, in cortical organotypic cultures treated with either pBDNF-Met66 or pBDNF-Val66 and quantified two aspects of PV cell axonal innervation: 1) perisomatic innervation around individual pyramidal cell somata visualized by NeuN immunostaining, and 2) the extent of pyramidal neurons innervated by a single PV cell. Our preliminary data show that pBDNF Met66 has a more severe effect on the maturation of PV cell innervations than pBDNF Val66. Excessive PV synapse pruning might contribute to the higher risk of developing psychiatric disorders associated with the presence of Val66Met.

2-A-11 *Perinatal high fat diet alters maternal milk miRNA expression and programs the DNA methylome in the amygdala.*

Sanoji Wijenayake[1], Sameera Abuaish[1], Wilfred de Vega[1], Christine Lum[1], Aya Sasaki[1], Patrick McGowan[2]

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

Perinatal high fat diet (HFD) induces epigenetic programming of DNA methylation and microRNA (miRNA) in rodent offspring. Recently, maternal milk was found to contain functional miRNA that can travel across offspring's intestinal endothelium post-ingestion, and mediate post-transcriptional regulation in various tissues. Milk miR-148/152 family is of particular interest because they are regulators of DNA methyltransferases (DNMTs), enzymes that catalyze DNA methylation. Here, we measured miR-148/152 levels in stomach milk and the amygdala at postnatal day 7(P7), followed by DNMT expression, DNMT enzymatic activity, and global DNA methylation levels at P7 and adulthood (P90) in the amygdala of female offspring with perinatal HFD exposure. Reduced representation bisulfite sequencing (RRBS) was also used to map genome-wide methylation differences at P7 and P90. Interestingly, miR-148/152 levels decreased in stomach milk and the amygdala, whereas, DNMT expression, DNMT activity, and global DNA methylation increased at P7. On the contrary, DNMT activity and global DNA methylation had a decreasing trend at P90. RRBS and Gene Ontology (GO) analysis showed differentially methylated regions enriched in biological processes including nervous system development at P7 and P90 in

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response to perinatal HFD exposure. To our knowledge, this is the first study to investigate genome-wide DNA methylation effects of perinatal HFD in female offspring at two developmental stages and highlight a unique link to maternally driven miRNAs that could contribute to the programming effects.

2-A-12 *A literature curated resource of experimentally tested gene regulatory relationships relevant to brain development*

Eric Chu[1], Alexander Morin[1], Tak HC Chang[1], Aman Sharma[1], Chao Chun Liu[1], Tue Nguyen[1], Paul Pavlidis[1]

[1]University of British Columbia

The development of the brain is orchestrated by a complex transcriptional gene regulatory network. Genome-wide network models reconstructed using high-throughput genomic data have vast potential in identifying the etiology of neurodevelopmental disorders. Due to the lack of a reliable gold standard dataset of direct regulatory relationships, it is currently impossible to validate the accuracy of these predictions. We have undertaken the first large-scale attempt to assemble a database of experimentally tested direct regulator-target relationships with relevance to the developing brain by mining the published literature. For each regulatory relationship, we establish confidence by finding and integrating multiple lines of experimental evidence ranging from transcription factor (TF) perturbation, TF binding, to reporter gene assays. We have identified hundreds of regulatory relationships encompassing a handful of key regulators of brain development including Pax6, Sox2, and Pou5f1. Of all the regulatory relationships captured, approximately half are backed by both binding and reporter assays. To demonstrate a use case for this resource, we show that a set of putative targets regulated by Pax6 in the embryonic mouse brain, detected by intersecting publicly available ChIP-seq and TF knockout transcriptomic datasets, is significantly enriched for the target genes recorded in our database. In summary, we provide a set of experimentally tested regulatory relationships to support the development and validation of regulatory networks reconstructed using high-throughput approaches.

2-A-13 *A role for Rho GTPases in retinoic acid-induced growth cone guidance*

Alysha Johnson[1], Gaynor Spencer[1]

[1]Brock University

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During the period of neuronal development, neurons must make correct synaptic connections with their appropriate targets. Growth cones are essential for axon pathfinding and target cell selection by sensing and integrating numerous guidance cues from their environment. Retinoic acid, the active metabolite of vitamin A, is an important regulator of neurite outgrowth during vertebrate development, but there is substantial evidence that it also plays a role in axon guidance. However, very little is known about the intracellular pathways activated by retinoic acid that induce changes in growth cone behaviour. Our previous studies have shown that retinoic acid-induced growth cone turning of invertebrate motoneurons requires local protein synthesis and calcium influx, similar to other known guidance cues in the central nervous system. However, the signalling pathways that link calcium influx to the regulation of cytoskeletal dynamics involved in growth cone turning are not currently known. We now present evidence that the intracellular pathways downstream of retinoic acid likely involve the Rho GTPases, Rac and Cdc42, and are currently examining potential effectors of calcium that may act on these GTPases. These studies will advance our knowledge of the mechanisms underlying growth cone pathfinding by retinoids during nervous system development and regeneration.

2-A-14 *A time course for cell maturation in the adult naked mole-rat brain*

Troy Collins[1], Mariela Faykoo-Martinez[1], Arthur Cheng[2], Christopher Lowden[2], Hai-Ying Cheng[2], Melissa Holmes[2]

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

Naked mole-rats are small, approximately mouse-sized, eusocial rodents that are extremely long-lived: living up to 30 years in captivity. Time to maturation of adult born neurons varies across species and is positively associated with lifespan. The objective of this study was to characterize the timeline of naked mole-rat adult neurogenesis from cell division to maturation. Male and female (n=24 each) age-matched adult non-breeding naked mole-rats were injected daily with the cell division marker 5-ethynyl-2'-deoxyuridine (EdU) for 7 days. Brains were then collected either 1 week, 3 weeks, 3 months, or 5 months (n=12 each) after the last EdU injection. Brains were stained for triple-label immunofluorescence for EdU, NeuN (a neuron-specific nuclear protein expressed by mature neurons) and doublecortin (DCX, a microtubule associated protein expressed by immature and migrating neurons). The number of EdU , EdU /DCX , and EdU /NeuN cells were counted in the subventricular zone (SVZ) and olfactory bulb (OB) at each time point. One-way analyses of variance were used to compare counts across time points and post hoc comparisons were done with Tukey's HSD. In the SVZ, EdU and EdU /DCX cells peaked at 1 week whereas no EdU /NeuN cells were detected. In the OB, significantly more EdU /DCX cells were present at 1 week than 3 months while EdU /NeuN cells were visible in the 3 month group. These results suggest that neuronal maturation takes up to 3 months in the adult naked mole-rat brain, consistent with other long-lived mammals including primates.

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2-A-15 *The effects of neuronal nitric oxide synthase and apoptosis on neural stem cell proliferation within the adult enteric nervous system*

Catherine Parisien[1], Alan Lomax[1]

[1]Queen's University

Inhibition of neurotransmission affects proliferation of neural stem cells (NSCs) within the adult central nervous system. While the adult enteric nervous system (ENS) contains NSCs, it was thought that they remained quiescent postnatally. It has recently been proposed that the adult ENS is in constant equilibrium between neuronal apoptosis and neurogenesis. We hypothesised that manipulating neurotransmission would lead to enteric NSCs becoming mitotically active and forming new neurons. Organotypic culture of myenteric plexus (MP) from mouse colon was performed for one week while inhibiting both neuronal nitric oxide synthase (nNOS) and caspase-3 mediated apoptosis. Neurons generated during culture from proliferating ENSCs were identified as cells that contained the proliferation marker 5-ethynyl-2-deoxyuridine (EdU) and the neuronal protein HuC/D. Neurons per ganglia were quantified by counting HuC/D-immunoreactive cells. Inhibition of nNOS with 7-nitroindazole (30μM) led to a ~250% increase in EdU-positive neurons, while there was no effect on the number of neurons per ganglia. Inhibition of Caspase-3 mediated apoptosis with zVAD-fmk (80μM) caused a ~50% increase in neurons per ganglia, with no increase in EdU positive neurons. Inhibiting both caspase-3 mediated apoptosis and nNOS led to a 200% increase in EdU-positive neurons, and a 100% increase in neurons per ganglia. These findings suggest that nitric oxide-induced suppression of neurogenesis and caspase-dependent neuronal apoptosis play important roles in maintaining the adult ENS.

2-A-16 *Shedding light on topographic map formation with GCaMP-expressing Xenopus tadpoles*

Vanessa Li[1], Anne Schohl[1], Edward Ruthazer[1]

[1]McGill University

Topographic maps constitute an important basis for the organization of sensory information in the brain. Sensory maps are known to undergo activity-dependent anatomical refinement during development, but little is known about functional changes in early maps. The Xenopus laevis retinotectal system permits the study of topographic map formation from very early stages. Tadpoles expressing the genetically-encoded calcium indicator GCaMP6 were obtained either by fertilizing eggs from albino frogs with sperm from elav:GCaMP6s transgenic frogs, or by microinjecting GCaMP6 mRNA into one blastomere of two-cell stage embryos. The latter approach results in tadpoles expressing GCaMP6 protein in the ipsilateral postsynaptic tectal

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neurons and the contralateral presynaptic retinal ganglion cell terminals, allowing independent analysis of pre- and postsynaptic map maturation. Retinotopic maps were extracted by presenting monocular visual mapping stimuli while performing rapid 4D multiphoton calcium imaging throughout the tadpole optic tectum, then correlating fluorescence intensity changes to the positions of visual stimuli. The contribution of NMDA receptors to map refinement was tested by comparing maps in tadpoles reared in presence of the NMDA receptor co-agonist D-serine or the non-competitive antagonist MK-801. We found that coarse retinotopic maps were already present at very early stages (NF stage 45). Rearing tadpoles in either MK-801 or D-serine did not prevent the emergence of retinotopic maps, but appears to have caused consistent alterations of the overall map organization.

2-A-17 *Abnormal social communication in infant IgSF21 mutant mice*

Nicole Pickett[1], Ryan Wheeler[1], Yusuke Naito[2], Hideto Takahashi[2], Tamara Franklin[1]

[1]Dalhousie University, [2]McGill University

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that results in social deficits and impairments in communication. Normal development of the neuroligin (NLGN)-neurexin (NRXN) pathway is integral to social communication across species, and the impairment of this pathway is thought to play a significant role in many cases of ASD. Immunoglobulin superfamily member 21 (IgSF21), a synaptic protein newly discovered to interact with neurexin-2-alpha, is important for synaptic differentiation in GABA-mediated inhibitory synapses. The relationship between IgSF21 and the NLGN-NRXN pathway suggests that mice lacking IgSF21 may exhibit a similar phenotype to existing mouse models of ASD and may therefore be a candidate for research on the disorder. In the current study, we measured maternal separation-induced ultrasonic vocalizations (USVs) in IgSF21-/-, IgSF21+/- and IgsF21+/+ mice from postnatal day six (P6) to twelve (P12). We observed that expression of IgSF21 significantly impacts the number of calls made as a result of maternal separation, with IgSF21 knockouts producing the lowest number of calls and IgSF21 heterozygotes producing the highest number of calls. These differences in call rate were not found to be driven by amplitude, frequency, or duration of calls. The findings of this research suggest an important role for IgSF21 in early social communication.

2-A-18 *Regulation of oligodendroglial proliferation and differentiation by NAD+-dependent deacetylase Sirtuin 2*

Kendra Furber[1], Merlin Thangaraj[1], Katie Ovens[1], Shaoping Ji[2], Martin Larsen[3], Adil Nazarali[1]

[1]University of Saskatchewan, [2]Henan University, [3]University of Southern Denmark

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The NAD+-dependent deacetylase Sirtuin 2 (SIRT2) is highly expressed in myelinating glia. Expression of SIRT2 in the central nervous system is up-regulated during postnatal stages of myelination. We have previously shown SIRT2 as a key regulator of oligodendrocyte differentiation in vitro; however, the molecular function of SIRT2 in myelination remains speculative. Here, we show Sirt2-/- mice display hypomyelination during postnatal development in vivo. Loss of Sirt2 decreased the extent of oligodendrocyte progenitor proliferation and delays differentiation. Transcriptomic and proteomic strategies were employed to identify potential molecular targets of SIRT2. RNA-seq analyses showed down-regulation of genes involved in biological processes such as nervous system development, cell differentiation, cell projection organization and cell-cell adhesion. Isolation and identification of acetylated peptides from cortical tissue from Sirt2-/- and C57BL/6 mice indicates that SIRT2 may interact with multiple partners at different stages of postnatal development to regulate myelination.

2-A-19 *A fetal fMRI study investigating the activation of the developing primary auditory cortex*

Estee Goldberg[1], Charles McKenzie[1], Barbra de Vrijer[1], Roy Eagleson[1], Sandrine de Ribaupierre[1]

[1]Western University

Fetal brain functional magnetic resonance imaging (fMRI) is typically limited to resting state fMRI, however, resting states can be influenced by multiple factors, including whether the fetus is awake or sleeping, or hypercapnia. Previous studies have employed auditory task fMRI, with an external sound stimulus directly on the abdomen of the mother; but recently there have been methodological and ethical concerns raised about that type of stimulus and a recommendation to not continue this method. We postulate that having the mother sing, as the auditory stimulus, would also result in activation in the fetal primary auditory cortex. Seven volunteers carrying singleton fetuses with a gestational age (GA) of 35-38 weeks underwent two task-based block design BOLD fMRI series. The data was segmented, and co-registered to the respective Computational Radiology Laboratory's GA fetal atlas. The segmented functional data were analyzed using SPM 12 (v7219) as a task fMRI ($p < 0.05$). Each region was overlaid onto the activation map to determine which areas in the brain had activation during task phases. Our preliminary results suggest that there are 22 regions consistently activated by the seven fetuses when exposed to the acoustic stimulus. Specifically, regions known to be part of the auditory network such as the right Heschl's gyrus, the right and left middle cingulate cortex and the left putamen. This preliminary study demonstrates that having the mother sing for blocks of time, one can activate and image the auditory network of the fetus.

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B - Neural excitability, synapses, and glia: Cellular mechanisms

2-B-20 *Spike initiation properties of pyramidal neuron axons revealed by channelrhodopsin-based photostimulation*

Mohammad Amin Kamaleddin[1], Stéphanie Ratté[1], Steven Prescott[2]

[1]University of Toronto; The Hospital for Sick Children, [2]University of Toronto

Spikes can be initiated in different parts of a neuron. In pyramidal neurons, spikes normally originate near the soma, in the axon initial segment (AIS), because this is the most excitable region of the neuron. The AIS converts sustained depolarization into repetitive spiking. Recordings from the cut end of axons (i.e. blebs) have suggested that axons do not spike repetitively during depolarization but, instead, spike only at the onset of abrupt depolarization. This transient spike pattern is consistent with class 3 excitability and is well suited for supporting spike propagation, but it remains unclear whether transient spiking accurately reflects axon excitability or is an artifact of axon damage. Recording intracellularly from an intact axon is prohibitively difficult because of its small caliber. To overcome this technical challenge, we evoked spikes from different parts of CA1 pyramidal neurons using localized photoactivation of channelrhodopsin-2 (ChR2) while recording the resulting spike train at the soma. We found that photostimulation of the soma evoked repetitive spiking, like during current injection, whereas photostimulation of the axon several hundred microns from the soma often evoked variable patterns of spiking. Careful dissection of those spike pattern revealed that only the first spike originated in the axon whereas later spikes were due to stray light exciting the soma and/or dendrites. Overall, our results confirm that axons spike transiently in response to sustained depolarization, consistent with class 3 excitability.

2-B-21 *Single cell eukaryote Salpingoeca rosetta communicate using neuron-like action potential spikes within rosette colonies involving Nav2 sodium and Cav1 calcium channels*

Jack Moffat[1], Prashanth Velayudhan[1], Amrit Mehta[1], Vu Son Luong[1], Noor Helwa[1], Reza Ramezan[1], Paul Marriott[1], J David Spafford[1]

[1]University of Waterloo

Marine, colony forming choanoflagellate, Salpingoeca rosetta is the simplest known eukaryote to possess sodium (Nav2) and calcium (Cav1) channels. These choanoflagellates transform into multicellular "rosettes" from singulates because of lipids secreted by a commensal bacteria, Algoriphagus. Choanoflagellates were grown on multielectrode array plates for recording. Choanoflagellates produced spontaneous extracellular field potentials of ~ 1 per 3 seconds with variable spike widths. No measureable field spike activity was measured in the absence of bacteria or without choanoflagellates cultures. Our preliminary data suggest that the "rosette" colonies are

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associated with the development of nervous system-like electrical communication. Transfected and recorded choanoflagellate SroCav1 channels in HEK-293T cells mediate highly, calcium selective ionic currents, possessing biophysical properties highly resembling human Cav1.2 channels with the exception of lacking calcium-dependent inactivation. Expressed choanoflagellate SroNav2 channels possess slow, non-selective channels. We have created the fast, highly-sodium selective Nav1 phenotype onto SroNav2, by replacement of a single pore residue and the III-IV linker from human Nav1.2. We are developing this unique model to examine the development of sodium and calcium ion dependent communication induced by multicellularity. This is the only model that we are aware of where the ionic communication between intact eukaryotes can be monitored in their native state, without perturbation on a multielectrode array.

2-B-22 *Ion channel correlations emerge from the homeostatic regulation of multiple neuronal properties*

Jane Yang[1], Steven Prescott[1]

[1]University of Toronto

Neurons must maintain multiple properties amid internal and external fluctuations. Failure of neuronal homeostasis may contribute to many neurological disorders (e.g. neuropathic pain and epilepsy). Previous work simulating homeostatic plasticity as activity-dependent co-regulation of ion channels showed that the relative rates of regulation explain correlations that emerge between regulated ion channels (O'leary et al. 2015, Neuron 88:1308). But we hypothesized that ion channel correlations also depend on other factors not previously considered, including the need to maintain >1 neuronal property. To investigate this, we implemented a simple model of O'leary's homeostatic rule to adjust up to five conductances to maintain rheobase alone or rheobase plus another property like ATP per spike. We found that ion channel correlations weakened as N, the number of tunable conductances, was increased whereas correlations strengthened as M, the number of regulated neuronal properties, was increased. Strong correlations were observed when M equals N - 1, even when ion channel combinations yielding the desired solution were found by means other than the homeostatic learning rule. Our results demonstrate that maintaining multiple neuronal properties requires up or downregulation of many ion channels, and that ion channel correlations emerge especially when there is a limited number of tunable ion channels relative to the number of neuronal properties requiring regulation.

2-B-23 *CRISPR-based approaches to explore interplay between the primate-specific long noncoding RNA LINC00473 and CREB*

Brandon S. Smith[1], Kirill Zaslavsky[2], James Ellis[2], P. Joel Ross[1]

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[1]University of Prince Edward Island, [2]The Hospital for Sick Children

Many of ~16,000 long noncoding RNAs (lncRNAs) encoded in the human genome are primarily expressed in the brain, but their neuronal functions remain largely unexplored. To prioritize lncRNAs for functional analyses, we performed global gene expression analyses to identify lncRNAs that are regulated by neuronal activity. Depolarization of human induced pluripotent stem cell-derived neurons promoted expression of activity-dependent protein coding genes like NR4A2, SIK1, FOS, and EGR1, and robustly induced the primate-specific lncRNA LINC00473 (LNC473). LNC473 is known to be regulated by the activity-dependent transcription factor CREB, and has also been implicated in CREB-dependent gene expression. To directly test the role of LNC473 in regulating CREB targets, we used CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa) to repress or promote transcription of the endogenous LNC473 gene. We designed 4 guide RNAs to target the LNC473 promoter and then tested their efficacy in doxycycline-inducible CRISPRi and CRISPRa in a human cell line. This approach revealed a negative correlation between expression of LNC473 and CREB target genes NR4A2 and SIK1, but no relationship between LNC473 and the CREB-independent SRF target EGR1. Having established a platform for functional genetic manipulation of LNC473, we next plan to test the roles of this lncRNA in CREB-dependent gene expression and structural plasticity in human neurons. Exploring neuronal functions of LNC473 may provide insights into both lncRNA biology and primate-specific mechanisms of neuronal gene regulation.

2-B-24 *Role of an aromatic-aromatic interaction in the assembly and trafficking of the zebrafish panx1a membrane channel*

Ksenia Timonina[1], Anna Kotova[1], Christiane Zoidl[1], Georg Zoidl[1]

[1]York University

Non-covalent aromatic-aromatic interactions are a force involved in the folding and stabilization of membrane proteins. Pannexin-1 is a ubiquitously expressed protein forming large pore membrane channel from hexameric units. A single pannexin-1 subunit has four transmembrane domains, two extracellular loops, a cytoplasmic loop, and intracellular amino and carboxyl terminals. Presently, the exact structure, folding, and assembly into pannexin-1 channels remains poorly understood. We noticed two highly conserved aromatic residues Trp123 and Tyr205 in the transmembrane domains 2 and 3 of the zebrafish pannexin-1a (panx1a). Our goal was to explore the role of these amino acids in aromatic-aromatic interactions governing the trafficking and stabilization of panx1a in the neuroblastoma cell line Neuro2a. Our results showed that mutations of these residues resulted in a protein that was able to undergo limited post translational modifications. However, the mutations caused a retention of panx1a in intracellular compartments. Using FRET and pull-down experiments, we proved that both mutants failed to interact with wild-type panx1a subunits. Further, FRAP and dye uptake assays showed that this behavior could be

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rescued by substituting residues for another aromatic amino acid. A complete restoration of protein trafficking and activity was achieved. These results provide insight into the mechanism of structural stabilization and folding of the panx1a membrane channel.

2-B-25 *Synaptic activity-dependent changes in the hippocampal palmitoyl-proteome*

Nusrat Matin[1], Glory Nasseri[1], Kyung-Mee Moon[1], Greg Stacey[1], Leonard Foster[1], Shernaz Bamji[1]

[1]University of British Columbia

Post translational palmitoylation of proteins involves the reversible addition of the fatty acid, palmitate, to substrate proteins. Emerging evidence suggests that palmitoylation is disrupted in a number of neurodevelopmental and neurodegenerative disorders. Indeed, of the 23 enzymes that mediate palmitoylation (collectively termed DHHC enzymes), loss of function mutations in 9 DHHC enzymes have been associated with schizophrenia, intellectual disability, Alzheimer's and Huntington's disease. Moreover, >41% of all synaptic proteins are substrates for palmitoylation. As impaired synaptic function is strongly associated with these disorders, we hypothesize that disruption in palmitoylation of synaptic proteins could impair synapse function and may be an underlying cause of these disorders. Differential palmitoylation of a handful of synaptic proteins have previously been observed in response to increased synaptic activity, suggesting that this post-translational modification may be important for the plasticity of synaptic connections. However, a more comprehensive proteomic analysis of all proteins that are differentially palmitoylated following increased synaptic activity is lacking. Using a proteomic approach, we have identified synaptic proteins that are differentially palmitoylated in the hippocampus following context-dependent fear conditioning. We have validated top hits and are currently evaluating the role of palmitoylation in regulating the function of synaptic proteins and their impact on synapse plasticity.

2-B-26 *Schizophrenia related protein Fxr1 controls homeostatic tuning of synaptic strength*

Jivan Khlghatyan[1], Alesya Evstratova[2], Simon Chamberland[3], Aleksandra Marakhovskaia[2], Tiago Soares Silva[2], Katalin Toth[1], Valerie Mongrain[4], Jean-Martin Beaulieu[2]

[1]Université Laval, [2]University of Toronto, [3]New York University, [4]Université de Montréal

Mental illnesses such as schizophrenia (SZ) and bipolar disorders (BD) are believed to be associated with a miss-regulation of neuronal activity homeostasis. Genetic variants of the fragile X mental retardation syndrome-related protein 1 (FXR1) are associated with mood regulation, SZ,

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and BD. However, the role of Fxr1 in the regulation of synaptic functions remains elusive. In vitro, Fxr1 expression was decreased during homeostatic synaptic upscaling, with no changes during downscaling. Augmentation of Fxr1 expression was sufficient to completely abolish upscaling and had no effect on downscaling. Furthermore, CRISPR/Cas9 knockout of Fxr1 induced a multiplicative upscaling phenotype regardless of TTX treatment. Translatome profile of control and Fxr1 overexpressing neurons during upscaling revealed molecular underpinnings of regulatory action of Fxr1. In mPFC, higher synaptic strength during enforced wakefulness was accompanied with a low expression of Fxr1. Similar to upscaling, augmentation of expression of Fxr1 abolished differences in synaptic strength between control and enforced wake mice. Translatome profile of control and Fxr1 overexpressing mPFC neurons during sleep and enforced wake revealed molecular players and networks impacted by Fxr1. Moreover, this allowed drawing large scale unbiased comparisons for Fxr1's mode of action during scaling and sleep/wake cycle. These results underscore a central role of Fxr1 during homeostatic regulation of synaptic strength in vitro and in vivo and suggest how it can contribute to illnesses like mood disorders and SZ.

2-B-27 *Investigating interneuron subtype-specific inhibitory spike-timing dependent plasticity in the primary motor cortex.*

Xinyi Liang[1], Jessica Pressey[1], Melanie Woodin[1]

[1]University of Toronto

Activity-dependent plasticity of synaptic connections between neurons is crucial for cortical circuit function in the developing and mature brain. Spike-timing dependent plasticity (STDP) is one form of plasticity where the precise timing of pre-synaptic and post-synaptic activity can induce long-term potentiation (LTP) or long-term depression (LTD). Previous studies of plasticity have been primarily focused on excitatory synaptic connections, while the plasticity of inhibitory connections is much less understood. Recent studies examined inhibitory STDP in auditory cortex and sensory cortex, but it is unknown whether STDP rules also apply to the motor cortex. It is known that local inhibitory neurons are involved in regulating the specificity of learning-related changes in synaptic circuits during motor learning. Considering the abundance of inhibitory interneurons, here we focus on parvalbumin-expressing interneurons (PV-INs) and somatostatin-expressing interneurons (SOM-INs). In order to examine STDP of inhibitory synapses onto layer 5 (L5) neurons in acute slices of mouse primary motor cortex (M1), we used viral-mediated delivery of channelrhodopsin-2 expressed in PV-Cre or SOM-Cre mice. Our results indicate coincident pre- and post-synaptic activity increase the strength of γ-aminobutyric acid (GABA)A-mediated inhibition from PV-INs onto L5-M1 pyramidal neurons by hyperpolarizing the reversal potential for GABA. Thus, we conclude that inhibitory STDP may function to regulate neuronal circuit function in the motor cortex.

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2-B-28 *The stability of glutamatergic synapses is independent of activity level, but predicted by synapse size*

Dylan Quinn[1], Sydney Harris[1], Michael Wigerius[1], Annette Kolar[1], James Fawcett[1], Stefan Krueger[1]

[1]Dalhousie University

Neuronal activity is thought to drive the refinement of developing circuits. However, its precise function in the formation and elimination of glutamatergic synapses leading to circuit refinement has remained controversial. To clarify the role of activity in synapse refinement, we have assessed the effects of chronic attenuation or complete block of glutamate release from a sparse subset of cultured hippocampal neurons on synapse turnover. Sustained chemogenetic attenuation of neurotransmission through presynaptic expression of a designer receptor exclusively activated by designer drugs (DREADD) had no effect on the formation or elimination rates of glutamatergic synapses. Sparse expression of tetanus neurotoxin light chain (TeNTLC), a synaptobrevin-cleaving protease that completely abolishes neurotransmitter release, likewise did not lead to changes in the rate in synapse elimination, but reduced the rate of synapse formation. The stability of active and silenced synapses correlated with measures of synapse size. While not excluding a modulatory role in synapse elimination, our results demonstrate that synaptic activity is neither required for the removal nor the maintenance of glutamatergic synapses between hippocampal neurons. Our findings also indicate that a form or degree of neurotransmitter release that is inhibited by TeNTLC but unaffected by DREADD inhibition facilitates the formation of glutamatergic synapses.

2-B-29 *L-type voltage gated calcium channels are necessary to induce mGluR dependent long term depression and this role is chronically altered following early life seizures*

Paul Bernard[1], Anna Castano[2], Timothy Benke[2]

[1]Atlantic Veterinary College, University of Prince Edward Island, [2]University of Colorado

Adult rats have chronically enhanced mGluR-mediated long-term depression (mLTD) following early life seizures (ELS). We explored the role of calcium influx and release in the expression of mLTD and how this is impacted by ELS. ELS were induced in rats at P7 with kainate (2 mg/kg). Hippocampal electrophysiological recordings were conducted at P60 using induction paradigms designed to isolate mLTD. Isradipine, BayK, PKI and CPA were used to probe the dependence on mLTD on calcium-related signaling. Blocking L-type voltage gated calcium channels (LTCCs) with isradipine completely blocked mLTD in controls and normalized enhanced mLTD following ELS.

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BayK, an agonist of LTCCs, increased mLTD in controls only; no further increase in mLTD was observed following ELS. CPA, which inhibits the release of calcium from intracellular stores, normalized mLTD following ELS and had no effect on mLTD in controls. In contrast, PKI, which regulates the activity of LTCCs, normalized mLTD following ELS, while also reducing mLTD in controls. Our results indicate that calcium flux through LTCCs is necessary for mLTD under normal conditions. ELS results in chronic alterations in the role of LTCCs in mLTD. Following ELS, chronically enhanced mLTD can be rescued using pharmacological methods to limit intracellular calcium, either via reducing LTCC activity or reducing the availability of intracellular stores. We have previously linked enhanced mLTD with deficits in social behavior, learning and memory. Future investigations will determine if normalizing calcium signaling in vivo normalizes behavior.

2-B-30 *Modeling myelin plasticity and its mechanisms of oscillatory brain synchronization*

Seong Hyun Park[1]

[1]University of Toronto

Glial cells form myelin, which play a critical part in brain function by facilitating the timely transmission of neural signals. Coherent synchronous activity in a vertebrae's nervous system strongly relies on a precise temporal structure of conduction delays across groups of neurons, which is mainly influenced by axon length and conduction velocity. For instance, it is found that impairment to myelin structure is linked to dysfunctions such as dyslexia and epilepsy. Despite its relevance, the network distribution of conduction velocities is not adequately considered in most computational models, as the delays are usually computed on the basis of a constant conduction velocity or ignored altogether. As a prototype to capture such network dynamics and to set the stage for the mathematical study of white matter plasticity, we expand on a canonical coupled Kuramoto oscillator model to include distributed delays. The aim is to establish how this model's interaction parameters and delay distribution affect its ability to exhibit a prominent oscillation. We propose a derived set of stability equations to provide a rigorous criterion under which this model's system achieves stable phase synchronization. As a result of numerical simulations, we obtain consistency between numerical results and the conditions set by the stability equations. We hope that these results lay out the groundwork to study the influence of time and activity dependent alterations in time delay distribution as well as to connect these findings with experimental data.

2-B-31 *Measurement and state-dependent modulation of the excitability of a brainstem motoneuron pool in-vivo*

Jasmin Aggarwal[1], Wen-Ying Liu[2], Gaspard Montandon[3], Hattie Liu[1], Richard Horner[1]

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[1]University of Toronto, [2]Fudan University, [3]St. Michael's Hospital

Measuring and modulating the excitability of a central motoneuron pool in-vivo to identify mechanisms of control is difficult and studies are few. Here we optically stimulate genetically targeted motoneurons to determine net excitability from measures of electromyogram output. We apply this approach to a motor circuit critical to the pathogenesis of obstructive sleep apnea (OSA). OSA is caused by airway closure in sleep due to relaxation of tongue muscles whose activity normally keep the airway open. The hypoglossal motor nucleus (HMN) is the source of motor output to the tongue. Studies were performed on mice expressing channelrhodopsin-2 exclusively on cholinergic neurons (n=22). Light pulses applied to the HMN under isoflurane-induced anesthesia elicited increases in tongue motor output, with the magnitude of responses dependent on stimulation frequency and power. Stimulations applied during wakefulness and non-rapid eye movement (non-REM) sleep elicited larger motor responses than during REM sleep at powers of 3-20mW. Response thresholds were also consistently greater in REM sleep (10mW) compared to non-REM sleep and wakefulness (3-5mW). These results demonstrate that HMN excitability was reduced in REM sleep compared to non-REM sleep and wakefulness, providing insight into the mechanism mediating upper airway muscle hypotonia in sleep. Future studies can apply this protocol to assess whether interventions manipulating select proteins can modulate HMN excitability across sleep and wakefulness to identify viable targets to restore motor output in sleep to waking levels.

2-B-32 *Microcircuitry of the cortex: connectivity, strength, and short-term plasticity*

Tim Jarsky[1], Luke Campagnola[1], Stephanie Seeman[1], Alex Hoggarth[1], Lisa Kim[1], Travis Hage[1], Pasha Davoudian[1], Gabe Murphy[1], Christof Koch[1], Hongkui Zeng[1], Christopher Baker[1], Corinne Teeter[1], Stephan Mihalas[1], Jung Hoon Lee[1]

[1]Allen Institute for Brain Science

We seek to characterize the microcircuitry of the cortex in mouse and human using multipatch electrophysiology supplemented in mouse with 2-photon optogenetic circuit mapping. Using the approaches mentioned above, we quantify connection probability as a function of distance, synaptic strength, and short-term synaptic dynamics. We make use of a set of transgenic mouse lines that enable targetting of two cortical cell classes in the same experiment, and all combinations of connections among cortical cell classes across experiments. In human, we focus on the connections among excitatory neurons classified by their morphology. We rely on the dimensionality reduction that modeling can provide to quantify and compare differences in synaptic dynamics. We intend to share the data to facilitate the generation of accurate, integrative computer models of the cortex. This poster will summarize the results to date, of our systematic, large-scale effort, to characterize local connectivity in the cortex.

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2-B-33 *Phylogenetic assessment of protein interactions between pre-synaptic CaV2 calcium channels and the scaffolding protein RIM*

Alicia Harracksingh[1], Abdul Rahman Taha[1], Adriano Senatore[1]

[1]University of Toronto Mississauga

During synaptic transmission, voltage-gated calcium channels type-2 (CaV2) mediate transient influxes of Ca2+ into the cytoplasm upon depolarisation, moderating synaptic vesicle (SV) calcium sensor activation, fusion of SVs to the plasma membrane, and release of vesicle contents (i.e., neurotransmitters) into the synaptic cleft. A proposed mechanism for tethering CaV2 channels in nanometer proximity to SVs is through a direct one-to-one interaction, mediated by the scaffolding protein Rab3a-Interacting Molecule (RIM) that binds to both the distal C-terminus of CaV2 and the vesicular protein Rab3. Work done in both vertebrates (Chordata) and invertebrates (Arthropoda) suggests a conserved function for RIM at the synapse, where disruption of RIM function leads to loss of CaV2 channel accumulation at the active zone. Particularly, in Drosophila, whether CaV2 channel accumulation occurs through a direct interaction between CaV2-RIM has yet to be determined. Moreover, whether more basal animals who, in some cases, do not have synapses rely on the CaV2-RIM interaction for regulated exocytosis of SVs has not been addressed. Using a phylogenetic assessment of this interaction by way of in vitro co-immunoprecipitation, my work explores the presence or absence of an interaction between CaV2 channel C-termini and the RIM PDZ-domain in organisms spanning several Metazoan phyla, in hopes of shedding light on the conservation of molecular structure- function of CaV2 channels, and ultimately, the evolution of the synapse.

2-B-34 *Impaired tuning of afferent excitatory synapses of hippocampal fast-spiking interneurons by acute early life seizures*

Ting Ting Wang[1], Hongyu Sun[1]

[1]Carleton University

The neonatal period is characterized by a critical period for synaptogenesis and plasticity, in part mediated by a physiological imbalance between excitation and inhibition. This imbalance is thought to enhance the susceptibility of the immature brain to early-life seizures. In this study, we aim to investigate the effects of early-life seizures on the excitatory synapses of hippocampal fast-spiking (FS) interneurons. Early-life seizures were induced at postnatal day 10-12 in mouse pups. Using whole-cell patch-clamp recordings, we recorded CA1 FS interneurons based on their morphology and distinctive electrophysiological properties. We found that intrinsic membrane properties were unchanged in FS interneurons from 1h post-seizure mice compared with controls.

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However, AMPAR mediated spontaneous EPSCs showed a significant decrease in frequency while amplitude in FS interneurons was unchanged. We further identified that acute seizures significantly reduced the pair pulse ratio in the FS interneurons from post-seizure mice compared to control interneurons. In addition, the repetitive stimulation data showed an impaired short-term plasticity in the FS interneurons following acute seizures. These results together strongly suggest that acute seizures impair afferent excitatory synapses of hippocampal FS interneurons through presynaptic mechanisms and provide a potential synaptic mechanism mediating hippocampal neural circuit reorganization in early life epilepsy.

2-B-35 *Cannabidiol elevates the ratio of feedforward:feedback inhibition to dampen hippocampal activity propagation*

Simon Chamberland[1], Erica Nebet[1], Evan Rosenberg[1], Orrin Devinsky[1], Richard Tsien[1]

[1]New York University

Cannabis sativa L. derivatives are emerging as therapeutics for some forms of epilepsy, with one formulation being FDA approved for certain epilepsies. Cannabidiol (CBD) administration to patients with certain treatment-resistant epilepsies decreases the number and severity of seizures. However, the effects of CBD on neuronal activity and neuronal circuits remain obscure. Here, we show that CBD decreases the propagation of high-frequency activity in the CA1 region of the mouse hippocampus. This CBD action is abolished by GPR55 deletion or block of GABAergic transmission. The dampening of spike throughput was traced to disparate CBD effects on parvalbumin+ (PV) and somatostatin+ (SST) interneurons (INs): enhanced feedforward recruitment of PV-INs but attenuated feedback recruitment of SST-INs. CBD exerted diametrically opposite effects on intrinsic excitability: PV-INs became more excitable and SST-INs less. As a result, CBD simultaneously increased feedforward inhibition while reducing feedback inhibition, greatly elevating the feedforward:feedback inhibition ratio. Notably, the CBD-induced attenuation of high frequency spike throughput was mimicked by concomitant optogenetic drive of PV-INs. In contrast, tonic optogenetic stimulation of PV-INs favored the propagation of activity. Thus, in hippocampal CA1, it is input-dependent (on-demand) recruitment of PV-INs, but not their spontaneous firing, that suffices to dampen high-frequency activity propagation. CBD quieting of SST-INs further disinhibits PV-INs. These mechanisms may contribute to the anti-seizure effects of CBD.

2-B-36 *Long term depression induced by group I metabotropic glutamate receptors: the role of probability of release*

Thomas Sanderson[1], John Georgiou[1], Graham Collingridge[2]

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[1]Mount Sinai Hospital, [2]University of Toronto

Background: Long term depression (LTD) in the hippocampus can be induced by application of the group I metabotropic glutamate receptor (mGluR) agonist DHPG. This form of plasticity is of relevance to learning and memory as well as neurological disease. Conflicting evidence exists as to whether this form of plasticity is expressed by changes at the pre- or the post-synapse. For example, in acute slices, DHPG-LTD is accompanied by changes in paired pulse facilitation (PPF), indicating a decrease in the probability of neurotransmitter release (P(r)). However, imaging experiments have indicated that DHPG is also accompanied by AMPA receptor trafficking at postsynaptic sites. Hypothesis: Group I mGluR receptors are known to interact with NMDA receptors and so we investigated whether NMDARs are involved in modulating the locus of expression of DHPG-LTD. Methods: We performed electrophysiological recordings in organotypic hippocampal slices at DIV 12-21 obtained from P7 SD rat. Results and Discussion: When we added DHPG, in the absence of NMDAR blockade, we induced LTD which was accompanied by an increase in PPF (to 130 ± 10 % of baseline 30 min after DHPG washout, $p < 0.05$, $n = 10$), indicating a decrease in P(r) as has been previously found. Application of DHPG in the presence of the NMDAR antagonist L-689,560, however, yielded no changes in PPF despite a large magnitude of LTD being apparent. Depending on the conditions therefore, both pre-synaptic and post-synaptic changes can contribute to DHPG-LTD.

2-B-37 *Characterisation of the Autism Spectrum-related protein, PTCHD1*

Connie Xie[1], Paul Hamel[1]

[1]University of Toronto

The neurodevelopmental disorder, Autism Spectrum Disorder (ASD), affects 1.6% of the population and is characterized by impaired social interaction, repetitive behaviour, and restricted interests. PTCHD1 point mutations are found in a subset of patients with ASD. Despite this association, the PTCHD1 protein activities and subcellular location remain largely uncharacterised. Previous studies show that this 12-pass transmembrane protein can be found in dendritic spines when transiently expressed in hippocampal neurons. It's C-terminus, which contains a PDZ-binding motif, was also shown to bind synaptic proteins PSD95 and SAP102. In order to better understand PTCHD1 activity, we investigated its expression and protein-protein interactions. A yeast two-hybrid screen using the two extracellular loops of PTCHD1 identified Snapin and Cox11 as potential interactors. Interaction between full-length PTCHD1 and Snapin, Cox11, and SAP102, was confirmed with co-immunoprecipitations and BioID labelling assays. Furthermore, we used a neuronal model produced from retinoic acid-induced P19 cells to show that transiently-expressed Snapin and PSD95 colocalized with PTCHD1. We have found that PSD95 and PtchD1 were expressed throughout P19 neuronal differentiation. CRISPR-mediated knockout of specific regions of PtchD1 in P19 cells is currently in progress to determine its role in

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neuronal development and signalling, which may provide novel insights into the etiology of a poorly understood neuropsychiatric disease.

2-B-38 *Exploring the molecular and phenotypic properties of voltage gated calcium channels in Trichoplax adhaerens, an animal without synapses*

Julia Gauberg[1], Sally Abdallah[2], Adriano Senatore[1]

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

Most animals have three types of voltage gated calcium (CaV) channels, CaV1, CaV2, CaV3, which can overlap in function but also exhibit unique specializations which are highly conserved among phyla. For example, CaV1 channels are expressed in muscle where they drive excitation-contraction coupling, while CaV2 channels are expressed in nerve terminals where they drive excitation-secretion coupling for regulated exocytosis of neurotransmitters. Understanding the functional divergence of CaV channels is especially relevant for CaV1 and CaV2 channels, which may have arisen from an ancestral gene duplication. To gain a better understanding of the divergence of these channels, we are studying homologues from the most early-diverging animal to possess these genes, Trichoplax adhaerens. Remarkably, Trichoplax lacks synapses and muscle and yet demonstrates complex and coordinated motile behaviour, including feeding, chemotaxis, and phototaxis. Trichoplax has six functionally distinct cell types, including contractile and neuroendocrine-like cells. We are exploring whether Trichoplax CaV1 and CaV2 channels are expressed in these cells, and whether they provide them with "muscle-like" and "neuron-like" qualities. Furthermore, we have cloned the Trichoplax CaV1 and CaV2 channels for functional expression in vitro, permitting electrophysiological and proteomic studies. Our work will provide important insights into the evolution of Cav1 and Cav2 channel biophysical properties, cellular localization, and physiological functions.

2-B-39 *Role of insulin and pharmacological regulation of intraocular pressure on retinal ganglion cell dendrite regeneration in glaucoma*

Sana El Hajji[1], Nicolas Belforte[1], Heberto Quintero[2], Adriana Di Polo[2]

[1]Université de Montreal, [2]University of Montreal Hospital Research Center

Dendrite pathology and synaptic disassembly are the main features of many neurodegenerative diseases including glaucoma. To date, the capacity of neurons to regenerate dendrites is poorly understood. To fill this gap, we focus on retinal ganglion cells (RGCs), a population of long-projecting neurons that convey visual information from the retina to the brain. The selective death of RGCs is crucial in the pathophysiology of glaucoma, the leading cause of irreversible blindness

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worldwide. We have demonstrated that insulin, administered at a time when there is substantial dendritic arbor retraction, promoted remarkable dendrite regeneration after optic nerve injury. High intraocular pressure (IOP) is the most important risk factor for developing glaucoma. Using a mouse model of ocular hypertension, we showed RGC dendritic retraction and synapse loss at two weeks after glaucoma induction. Daily insulin eye drops promoted dendrite and synapse regeneration, without reducing IOP. Importantly, pharmacological reduction of IOP by itself was not sufficient to stimulate RGC dendrite regeneration. Our data suggest that endogenous insulin levels are not sufficient to promote RGC dendrite regeneration following reduction of IOP in glaucoma, and support the critical role of insulin administration to restore RGC connections and retinal function. Our current studies focus on the transcriptome of RGCs to identify molecular pathways involved in insulin-mediated dendritic and synaptic regeneration after axonal injury.

2-B-40 *Does spatial learning change synaptic expression of the insulin receptor?*

Saeideh Davari[1], Alyssa Guerra[1], John Mielke[1]

[1]University of Waterloo

Although insulin and its receptor are widely distributed throughout the brain, their roles remain unclear. While earlier work has shown that some neural insulin receptors (IRs) do regulate glucose metabolism, most neurons do not employ insulin-sensitive glucose uptake. Notably, a previous study found that spatial memory acquisition in rats correlated with an increased IR density in hippocampal synaptosomes. Herein, we have attempted to not only replicate this finding, but to also examine the effect with greater anatomical precision. Male, Sprague-Dawley rats at six weeks of age received four training trials over one day in the Morris Water Maze (MWM). Each trained rat was paired with a swim control animal that spent the same amount of time in the pool. All animals were sacrificed one hour after the final trial. The hippocampi were removed, and the dorsal and ventral regions were isolated to enhance the anatomical information gathered. Synaptoneurosomes, a preparation enriched in synaptic terminals, were prepared for each hippocampal region, and then probed for the Ò-subunit of the IR using standard immunoblotting techniques. Analyses of the MWM data revealed that the trained animals displayed a reduced path length and escape latency by the end of training. Having confirmed the acquisition of spatial memory, we are proceeding to assess IR density within tissue homogenates, and hypothesize that an increase will be seen in the dorsal region only. By clarifying their role in learning and memory, our work will help to further our understanding of neural IRs.

2-B-41 *Alternative splicing of the Nav1.5 voltage-gated sodium channel alters channel activation via two amino acid residues*

Adamo Mancino[1], Yuhao Yan[1], Mark RP Aurousseau[1], Derek Bowie[1]

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[1]McGill University

Voltage-gated sodium (Nav) channels are responsible for action potential upstroke across all excitable tissues. Given that there are nine distinct isoforms, each of which having its own pattern of alternative splicing, a large diversity of Nav channels exists to fulfill their many roles. One recurring site of alternative splicing is the S3-S4 extracellular linker in domain I. In most isoforms, alternate splicing at this site modifies channel inactivation, but, in Nav1.5, it shifts the voltage-dependence of channel activation. Given that the specific structure-function relationships are still not fully explored, we sought to examine alternative splicing in the domain I S3-S4 linker of Nav1.5 in more detail. We identified the two amino acid residues, aspartate/lysine-211 and threonine/serine-207, responsible for altered channel gating. Molecular dynamics simulations suggest that these exchanges distort the network of gating charges and counter-charges within the voltage sensor domain. Furthermore, disrupting the voltage sensor of each domain revealed a predominant role for domain I in setting the voltage-dependence of channel activation, explaining why this region may be subject to alternative splicing. Finally, we manipulated positions 211 and 207 in a related Nav channel isoform, Nav1.4, which revealed that the shift in activation was transferable to other Nav channels. Our study sheds light on the mechanism by which alternative splicing of domain I modulates the functional properties of Nav channels, which may in turn contribute to fine-tuning neuronal excitability.

2-B-42 *Contribution of novelty, blood metabolites and blood-brain barrier transport on extracellular brain glucose and lactate fluctuations during motor behavior*

Alexandria Beland[1], Caleb Routledge[1], Devon Frayne[1], Claude Messier[1]

[1]University of Ottawa

The relative contribution of glucose and lactate to neuroenergetics is a controversial topic. Despite this controversy, there is a plethora of evidence demonstrating the brains ability to take up and use blood lactate when it is in excess, during such conditions as increased physical activity. Physical activity is also capable of stimulating neuronal activity. Therefore, we aimed to examine the impact of systemic availability of metabolites and blood-brain barrier transport on extracellular fluctuations of glucose and lactate. Mice were subjected to various physical conditions, such as running and hanging on upside down, following systemic metabolite injections of either lactate, glucose, fructose or beta-hydroxybutyrate. These same conditions were additionally tested when blood-brain barrier GLUT1 (glucose) and/or MCT1 (lactate) transport were inhibited. Preliminary results suggest a consistent pattern of fluctuations, with motor behaviour inducing a rise in extracellular lactate and a decrease in extracellular glucose in certain behavioural conditions. These increases were attenuated by systemic injections of alternative fuels such as lactate. These results seem to suggest a compensatory mechanism of blood brain barrier transport when both

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transporters are inhibited, leading to larger increases in extracellular lactate when compared to the other conditions.

2-B-43 *Developmentally-regulated muscarinic receptor function in layer VI of the medial prefrontal cortex*

Ashutosh Patel[1], Myles St-Denis[1], Sierra Codeluppi[1], Craig Bailey[1]

[1]University of Guelph

Acetylcholine (ACh) receptors expressed on pyramidal neurons within layer VI of the rodent medial prefrontal cortex (mPFC) play an important modulatory role in prefrontal-dependent cognitive functions. This role is mediated by nicotinic receptors and muscarinic receptors (mAChRs). The objective of this study was to determine the contribution of mAChR isoforms toward the overall muscarinic response in these layer VI neurons. Whole-cell electrophysiological recordings were performed in mPFC layer VI neurons from young postnatal (postnatal day (P) 15-20) and adult (P60-100) mice of both sexes. Muscarinic responses to ACh application (1 mM, 30 s) demonstrated transient inhibition in a subset of neurons followed by a prolonged excitation. The ratio of neurons exhibiting transient inhibition, and the duration of this response, were significantly greater in young mice than in adult mice. Pharmacological experiments using isoform-selective antagonists demonstrated that both the M1 and M3 isoforms were required for the inhibition response in all groups, whereas the M2 isoform contributed to the inhibition response in male mice only. The M1 isoform contributed to the excitatory response in all groups, whereas the M2 and M3 isoforms contributed to the excitatory response in adult mice only. Semi-quantitative RT-PCR performed in isolated mPFC tissue revealed that mRNA expression for mAChR isoforms was greater in adult mice than in young mice. Ongoing experiments aim to determine whether the function of these mAChR isoforms correlates with the morphology of recorded neurons.

2-B-44 *Voltage-sensor domains contribute unequally to sodium channel activation and inactivation*

Yuhao Yan[1], Adamo Mancino[1], Niklas Brake[1], Takushi Shimomura[2], Yoshihiro Kubo[2], Anmar Khadra[1], Derek Bowie[1]

[1]McGill University, [2]National Institute for Physiological Sciences

Voltage-gated sodium (Nav) channels mediate the upstroke of the action potential across all excitable tissues. The Nav channel complex consists of four homologous domains, joined together in a single polypeptide chain. Since the four domains are nonidentical, they are thought to play distinct roles in channel gating. In particular, domains I through III have been associated with

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channel activation, whereas domain IV is thought to be responsible for inactivation. Here, we studied the role of each domain and its impact on the gating behavior of the Nav1.5 channel. Mutations that immobilize domains I and IV, but not II and III, significantly alter the voltage-dependence of channel activation. In keeping with this, voltage-clamp fluorometry revealed that the voltage sensors of domains I and IV move in a manner correlated with channel activation. In contrast, domain III is constitutively in a primed position, whereas movement of domain II is uncoupled from the gating process. Immobilization of each of the four domains promotes channel inactivation, with domains III and IV being most pronounced. Interestingly, co-expression of Nav1.5 with auxiliary β1 and β3 subunits attenuates inactivation in Nav1.5. Ongoing patch-clamp experiments and Markov modelling are exploring which Nav channel domain is targeted by auxiliary subunit regulation. Our study will provide a more comprehensive understanding of how each of the four non-identical domains contribute to Nav channel gating.

2-B-45 *Alpha5 nicotinic receptors in the prefrontal cortex: built to resist?*

Sridevi Venkatesan[1], Tianhui Chen[1], Yupeng Liu[1], Evelyn Lambe[1]

[1]University of Toronto

Layer 6 pyramidal neurons in the prefrontal cortex express the α5 nicotinic acetylcholine (ACh) receptor subunit encoded by Chrna5 which is critical for performing demanding attention tasks. However, cellular mechanisms by which the α5 subunit influences attention are unclear. We studied the α5 subunit's role in endogenous cholinergic modulation of the PFC by measuring layer 6 neuron responses to optogenetic release of ACh, in brain slices from WT and α5-/- mice. Initial results suggested that cholinergic responses are not different between WT and α5-/- cells. However, conditions that cause sustained activation of nicotinic receptors, such as prolonging ACh presence by blocking acetylcholinesterase with DFP unmasked major differences between the WT and α5-/-. Cholinergic responses in the WT increased after DFP due to prolonged activation of nicotinic receptors, but there were no significant changes in the α5-/-. Responses in WT neurons were also resistant to application of 100 nM nicotine, an intervention which abolished cholinergic responses in the α5-/- presumably due to desensitization of nicotinic receptors lacking the α5 subunit. This pattern suggests that the fundamental role of the α5 nicotinic receptor subunit in the prefrontal cortex is to protect receptors from desensitization- enabling them to be activated under prolonged ACh release, such as during intense attentional effort. Ongoing experiments are probing network level activation of layer 6 neurons by ACh and mechanisms of desensitization and resensitization of these vital prefrontal nicotinic receptors.

2-B-46 *Nitric oxide production from inducible nitric oxide synthase inhibits microglia proliferation via TRPV2-mediated calcium influx*

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Matthew Maksoud[1], Vasiliki Tellios[1], Wei-Yang Lu[1]

[1]University of Western Ontario

Background - Proliferation is regulated by calcium (Ca2+) influx and nitric oxide (NO). We have previously shown that NO induces transient receptor potential vanilloid type 2 (TRPV2) ion channel activity in microglia, which is associated with Ca2+ influx. Therefore, we set fourth to examine whether NO regulates microglia proliferation via TRPV2-Ca2+ influx. Methods - immunocytochemistry, Ca2+ imaging, and immunoblot were used to examine the effect of NOC-18 (100μM), a slow release NO-donor, on TRPV2-Ca2+ influx and cell cycle markers within microglia. Experiments were conducted on primary wildtype (WT) and inducible nitric oxide synthase knockout (iNOS-/-), as well as BV2 microglia. Results - The proliferative markers Ki67 and phosphorylated histone 3 (pH3) were expressed more in iNOS-/- microglia than WT microglia cultures. Furthermore, application of NOC-18 decreased Ki67 and pH3 expression in iNOS-/- microglia cultures. Within cultured BV2 microglia, a large TRPV2 mediated calcium influx occurs in cells lacking Ki67 and pH3 expression, while a significantly smaller TRPV2-Ca2+ influx was observed in BV2 microglia expressing pH3. Significantly more NFATC2 expression was observed in the nucleus of WT and iNOS-/- microglia treated with NOC-18 or the TRPV2 agonist probenecid, while TRPV2 inhibition using Tranilast attenuated nuclear NFATC2 localization from NOC-18 treatment. Conclusion - The available data suggests that NO inhibits microglia proliferation via TRPV2-Ca2+ influx inducing nuclear localization of the transcription factor NFATC2.

2-B-47 *Bergmann glia morphology and GLAST expression is downregulated in nNOS-/- mice*

Vasiliki Tellios[1], Matthew Maksoud[1], Wei-Yang Lu[1]

[1]University of Western Ontario

INTRO: Astrocytes prevent excitotoxicity by removing glutamate from the synaptic cleft and recycling it to the neuron for later use. Specialized cerebellar astrocytes, Bergmann glia (BG), predominately use glutamate/aspartate transporters (GLAST) for glutamate uptake. While it is unknown how GLAST is regulated in the cerebellum, dysfunction of this channel has been shown to result in neuronal death. Recently, nitric oxide (NO) has been shown to help upregulate GLAST function in vitro, but the mechanism of NO modulation is unknown. Therefore, this study aims to characterize the effects of NO on BGs using mice lacking neuronal nitric oxide synthase (nNOS-/-). METHODS: Immunohistochemistry and western blot (WB) will examine wildtype (WT) and nNOS-/- BG morphology and GLAST expression in mice aged 7 days, 14 days and 7 weeks. WB and staining will examine GLAST protein levels across development in ex vivo organotypic slice cultures and primary BG. RESULTS: Total GLAST expression in vivo was less in nNOS-/- cerebella compared to WT across all time points with staining and WB. Ex vivo WT slices treated with NOS

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inhibitor or nNOS-/- slices treated with slow release NO-donor NOC-18 showed a decrease and increase in GLAST compared to control, respectively. WT BGs treated with nNOS inhibitor showed a decrease in membrane expression, while nNOS-/- BGs treated with SNAP, or PKGi and SNAP, showed an increase and decrease in GLAST plasma membrane expression, respectively. CONCLUSION: This data suggests nNOS/NO signaling is necessary for GLAST expression on the plasma membrane in BGs.

2-B-48 *Inhibition of neuronal electrical excitability by a common flame retardant*

Anjelica Bodnaryk[1], Colleen Peterson[1], Tammy Ivanco[1], Gregg Tomy[1], Mark Fry[1]

[1]University of Manitoba

Many manufactured goods include flame retardant (FR) chemicals to inhibit ignition, however many commonly used FRs such as polybrominated diphenyl ethers (PDBEs) have recently come under scrutiny because of their environmental persistence, bioaccumulation and toxicity to organisms. Many PBDE congeners such as PBDE209 are banned by the Stockholm Convention because of these adverse effects. There has been a shift toward replacing potentially harmful PBDEs with other FRs such as 1,2-dibromo-4-(1,2-dibromoethyl) cyclohexane (TBECH). Although relatively new, recent studies suggest that TBECH is pervasive in the environment and biota, however little is known about its toxicology. Recent studies indicate TBECH is an endocrine disruptor and affects reproductive physiology and success via gene regulation and signalling pathways. In order to assess the acute neurobiological effects of TBECH, we have examined its effects on electrical activity of dissociated Lymnaea stagnalis neurons using current clamp and voltage clamp electrophysiology. Current clamp recordings indicate that TBECH affects resting membrane potential, action potential frequency and latency of the first action potential in a dose dependent manner, indicating an inhibiting effect on activity. Furthermore, voltage clamp experiments demonstrate that TBECH causes a reduction in transient and non-inactivating K+ currents, with non-inactivating K+ currents being most sensitive. Comparing the effects of TBECH and tetraethylammonium (TEA) revealed that TBECH blocks a subset of TEA-sensitive current.

2-B-49 *The effects of peripheral inflammation on seizure predisposition in a freeze-lesion model of focal cortical dysplasia*

Tarek Shaker[1], Bidisha Chattopadhyaya[2], Abdul-Rahman El-Hassan[2], Graziella Di Cristo[1], Lionel Carmant[1], Bénédicte Amilhon[1], Alexander Weil[1]

[1]Université de Montréal, [2]CHU Sainte-Justine Research Center/Université de Montréal

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Focal cortical dysplasia (FCD) is closely associated with epilepsy, yet, little is known about how FCD induces epileptogenesis. Recent studies reported neuroinflammation along with T cell infiltration in FCD lesions resected from epilepsy patients. Therefore, we hypothesized that FCD recruitment of T cells elicits neuroinflammation, which may elevate seizure susceptibility. To investigate this, we induced a freeze-lesion (FL) in the cortex (Cx) of postnatal day 1 (P1) rats to mimic FCD pathology. Following FL, we detected T cell infiltrates in the Cx co-immunolabeled with the pro-inflammatory cytokine precursor Caspase-1 (Casp1). Further, neurons in FL but not sham control Cx expressed Casp1, suggesting that T cells transduced peripheral inflammation to the Cx. To recapitulate FL-induced T cell migration in vitro, we incubated T cells derived from neonatal rats with lipopolysaccharide (LPS) and Nigericin (NG) immunogens for 6 hours (LPS+NG) to activate Casp1, then co-cultured T cells with organotypic cortical slices. Whole-cell patch recordings showed that cortical pyramidal neurons were notably more excitable when slices were co-cultured with LPS+NG T cells than with T cells treated with LPS only. Similarly, upregulation of Casp1 downstream effectors, such as ASC, in neurons was exclusive to slices co-cultured with LPS+NG T cells, indicative of Casp1-dependent crosstalk between T cells and neurons. We are currently testing whether delivering selective Casp1 inhibitors, e.g. VX-765, to FL rats in vivo or to T cell-Cx co-cultures in vitro can rescue T cell-induced effects.

2-B-50 *The role of hypocretin neurons in social stress*

Derya Sargin[1], Jaideep Bains[1]

[1]Hotchkiss Brain Institute

The physiological response to stress involves the release of a cascade of hormones under the control of the hypothalamic pituitary adrenal system. In addition to regulating the stress response, an important component of this system, the hypothalamus, also controls multiple homeostatic functions, including energy balance. The hypocretin/orexin neurons specifically located within the lateral hypothalamus have been studied primarily for their role in sleep/wakefulness and motivation for food intake. These neurons have synaptic connections with areas involved in the regulation of neuroendocrine stress response, emotion, fear and reward including the paraventricular nucleus of hypothalamus (PVN), dorsal raphe (DR), amygdala and nucleus accumbens (NAc). Recent work from our lab has shown that PVN-CRH neurons are critical both for the transmitting stress to others, and detecting stress in others. Given the extensive interconnections between hypothalamic nuclei, including a direct projection from PVN-CRH to the LH, a role of the hypocretin system in emotional regulation is not unexpected but it remains poorly understood. Here, using detailed behavioral analysis in combination with fiber photometry and optogenetics, we show that the hypocretin system is highly responsive to physical and social stressors. Ongoing work is focused on identifying the downstream targets of hypocretin neurons in stressful states.

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2-B-51 *Neurons and astrocytes control local brain blood flow on distinct timescales*

Adam Institoris[1], Cam Ha Tran[2], David Rosenegger[1], Govind Peringod[1], Grant Gordon[3]

[1]Hotchkiss Brain Institute, [2]Reno School of Medicine, University of Nevada, [3]University of Calgary

While astrocyte endfeet can regulate local blood flow by releasing vasoactive messengers, it is not clear how astrocytes contribute to functional hyperemia, where local synaptic activation is translated to arteriole dilation. We studied astrocyte function during various lengths of functional hyperemia. We imaged synthetic and genetically encoded Ca2+ indicators with 2-photon microscopy through a closed cranial window over the barrel cortex of awake mice. 5s air puff to the contralateral whiskers elicited neuronal Ca2+ responses prior to arteriole dilation, while astrocyte Ca2+ levels increased 2-3s later. 30s air puff elicited a larger arteriole dilation with prolonged astrocyte endfoot and process Ca2+ signals. In acute neocortical slices, low intensity, 5s electrical stimulation evoked neuronal Ca2+ elevation and vasodilation without astrocyte endfoot Ca2+ increase. Clamping intracellular Ca2+ concentration in the astrocyte network by patch-infusing BAPTA had no effect on short stimulation-induced vasodilation even at higher stimulation frequency and intensity. This purely neuronal response was mediated via AMPA receptors and partially by cyclooxygenase-2-derived prostaglandins, but blocking vasoactive pathways in astrocytes failed to reduce vasodilation. Surprisingly, intense stimulation for 30s activated astrocytes, and clamping astrocyte Ca2+ reduced arteriole dilation. Astrocyte-related vasodilation to enduring stimulation was mediated by epoxyeicosatrienoic acid. We propose that neurons initiate while astrocytes sustain vasodilation during functional hyperemia.

2-B-52 *The projection targets of medium spiny neurons govern cocaine-evoked synaptic plasticity in the nucleus accumbens*

Corey Baimel[1], Laura McGarry[1], Adam Carter[1]

[1]New York University

Repeated exposure to drugs of abuse alters neural circuits involving the nucleus accumbens (NAc). Medium spiny neurons (MSNs) are the principle cell type of the NAc, and can be divided into two broad subpopulations based on expression of dopamine 1 or 2 receptors, with drugs strongly rewiring inputs onto D1+ MSNs. Recent work highlights diversity within the D1+ MSN population, but whether drug-induced plasticity occurs in different cell types is unknown. Here we use anatomical tools, whole-cell electrophysiology, two-photon microscopy and optogenetics, to examine synaptic connectivity and cocaine-evoked plasticity at specific networks within the NAc medial shell. We first identify distinct subpopulations of D1+ MSNs that project to either the ventral

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pallidum (D1+VP) or the ventral tegmental area (D1+VTA). We then show how inputs from the ventral hippocampus (vHPC), but not the basolateral amygdala (BLA), are initially biased only onto D1+VTA MSNs. Lastly we show that repeated cocaine exposure eliminates this bias of vHPC inputs onto D1+VTA MSNs, while strengthening BLA inputs onto D1+VP MSNs. Together, our results reveal how circuitry and plasticity depend on the specific long-range projections of NAc MSNs.

2-B-53 *Intrinsic plasticity as a neural correlate for stress habituation*

Sara Matovic[1], Aoi Ichiyama[2], Hiroyuki Igarashi[3], Xue Fang Wang[4], Eric Salter[5], Mathilde Henry[6], Nathalie Vernoux[7], Marie-Eve Tremblay[7], Wataru Inoue[3]

[1]Robarts Research Institute, [2]Western University, [3]University of Western Ontario, [4]Robarts Research Institute, University of Toronto, [5]University of Toronto, [6]Université Laval, Université de Bordeaux (current), [7]Université Laval

Encountering a stressor activates the hypothalamic-pituitary-adrenal (HPA) axis, but this stereotypic neuroendocrine response often "habituates" and diminishes with repeated stress exposure. Neural plasticity mechanisms underlying HPA axis habituation remain unknown. Using a mouse model of repeated restraint and slice patch-clamp electrophysiology, we studied hypothalamic corticotropin releasing hormone neurons that form the apex of the HPA axis. We found that the intrinsic excitability of these neurons substantially decreased after daily repeated stress in a time course that coincides with their loss of stress responsiveness in vivo. This intrinsic plasticity change co-developed with an expansion of surface membrane area, resulting in a decrease in input conductance with little changes in conductance density. Moreover, repeated stress augmented surface irregularity on the plasma membrane, describing an ultrastructural plasticity that may efficiently accommodate membrane area increase. Overall, we report a novel structure-function relationship for intrinsic plasticity that correlates with the habituation of neuroendocrine response.

2-B-54 *Impact of Chrna5 deletion on habenulopeduncular neurotransmission*

Sanghavy Sivakumaran[1], Yupeng Liu[1], Tianhui Chen[1], Daniel Sparks[1], Evelyn Lambe[1]

[1]University of Toronto

The habenulopeduncular pathway has been implicated in nicotine aversion, but the cellular mechanisms of this aversion are unclear. Cholinergic ventral medial habenula (vMHb) neurons innervate interneurons in the interpeduncular nucleus (IPN), which present a multitude of nicotinic acetylcholine receptor (nAChR) subunits. Notably, the IPN has the strongest expression of the

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nAChR subunit α5 (Chrna5) in the brain, which is often linked to nicotine aversion. Here, we use whole cell electrophysiology and optogenetics in acute brain slices to investigate the neurophysiological role of the α5 nAChR subunit for endogenous habenulopeduncular signaling. Previously, we have shown that cholinergic vMHb neurons fire ~2Hz at baseline and increase to ~10Hz under strong stimulation, such as nicotine exposure. These cholinergic vMHb neurons also express VGLUT2 and employ glutamate as a neurotransmitter, the physiological mechanisms of which are poorly understood. For our experiments, we used transgenic mice to optogenetically activate habenular cholinergic neurons in mice deleted for Chrna5 (α5KO) and wildtype littermates. In both genotypes, activation of cholinergic afferents with channelrhodopsin induces excitatory postsynaptic currents in IPN cells, which are suppressed by glutamatergic antagonists. However, Chrna5-deleted mice show stronger habenulopeduncular neurotransmission than wildtype controls. Ongoing work is examining the impact of Chrna5 deletion on additional aspects of the habenulopeduncular pathway, including its nicotine sensitivity and aversion neurocircuitry.

2-B-55 *Cerebellar stellate cell excitability is coordinated by shifts in the gating behavior of voltage-gated Na+ and A-type K+ channels*

Ryan Alexander[1], John Mitry[1], Vasu Sareen[1], Anmar Khadra[1], Derek Bowie[1]

[1]McGill University

Neuronal excitability in the vertebrate brain is governed by the coordinated activity of both ligand- and voltage-gated ion channels. In the cerebellum, spontaneous action potential (AP) firing of inhibitory stellate cells (SCs) is variable, typically operating within the 5-30 Hz frequency range. AP frequency is shaped by the activity of somatodendritic A-type K+ channels and the inhibitory effect of GABAergic transmission. An added complication, however, is that whole-cell recording from SCs induces a time-dependent and sustained increase in membrane excitability making it difficult to define the full range of firing rates. Here, we show that whole-cell recording in cerebellar SCs of both male and female mice augments firing rates by reducing the membrane potential at which APs are initiated. AP threshold is lowered due to a hyperpolarizing shift in the gating behavior of voltage-gated Na+ channels. Whole-cell recording also elicits a hyperpolarizing shift in the gating behavior of A-type K+ channels which contributes to increased firing rates. Hodgkin-Huxley modeling and pharmacological experiments reveal that gating shifts in A-type K+ channel activity do not impact AP threshold, but rather promote channel inactivation which removes restraint on the upper limit of firing rates. Taken together, our work reveals an unappreciated impact of voltage-gated Na+ channels that work in coordination with A-type K+ channels to regulate the firing frequency of cerebellar SCs.

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2-B-56 *Diverse topography of voltage-gated Ca2+ channel clusters in distinct morphological modules of a central nerve terminal*

Adam Fekete[1], Yukihiro Nakamura[2], Yi-Mei Yang[3], Stefan Herlitze[4], Melanie D. Mark[4], David DiGregorio[5], Lu-Yang Wang[1]

[1]The Hospital for Sick Children, [2]Department of Pharmacology, Jikei University School of Medicine, [3]University of Minnesota, [4]Ruhr-University Bochum, [5]Unit of Dynamic Neuronal Imaging, Institut Pasteur

Clustering of voltage-gated Ca2+ channels (VGCCs) at active zones (AZ) defines local Ca2+ domains, a critical determinant of release probability (Pr) at release sites. However, presynaptic terminals typically contain multiple AZs with heterogeneous Pr, but the underlying mechanisms have not been described. We addressed this issue by using mature calyx of Held synapses typically containing 3-4 digit-like stalks, but variable number of bouton-like swellings which inversely correlate with global Pr of whole terminals (Grande and Wang, 2011). By tracing morphological complexity and distribution of VGCCs in stalk and swelling modules using a knock-in mouse line in which the N-terminus of P/Q-type VGCC alpha1 subunit was tagged with citrine, a GFP variant (Mark et al., 2011), we found that calyx complexity directly correlates with the number of VGCC clusters per calyx. The number of clusters is 40% higher on swellings than stalks, but the size of clusters is 35% larger on stalks. Smaller local [Ca2+] and lower Pr in swellings underpin the inverse correlation between complexity and global Pr. We considered a model in which the global Pr is the weighted average of Pr-s at distinct AZs and found that the simulated correlation between complexity and synaptic strength are comparable to that derived from experiments (Fekete et al., 2019). We concluded that local Pr is more critically dependent on the size than the number of VGCC cluster, and that global Pr can be diversified by the weighted average of Pr-s from multiple release sites within a central terminal.

2-B-57 *Deletion of complement cascade components C3 or Cd11b does not impact synapse strength or plasticity at schaffer collateral-CA1 synapses*

Eric Salter[1], Sun-Lim Choi[2], Liam Ralph[2], Gang Lei[2], Junhui Wang[2], Graham Collingridge[1]

[1]University of Toronto, [2]Lunenfeld-Tanenbaum Research Institute

Background: The complement cascade is an innate immune pathway that is a key regulator of synaptic pruning by microglia during development and is critical for proper brain wiring. Neuronal activity is able to regulate complement activation and synapse pruning by microglia, however the mechanisms linking neuronal activity to complement activation are completely unknown. Hypothesis: The complement cascade is necessary for the induction of NMDAR-LTD in the hippocampus. Methods: Using acute brain slice electrophysiology, we measured synaptic function at Schaffer collateral (SC) synapses from P13-17 mice with a genetic deletion of Cd11b or C3.

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We also measured the expression of excitatory synaptic proteins. Results: There was no difference in basal synaptic properties nor in the magnitude of LTP, NMDAR-LTD, metabotropic glutamate receptor (mGluR)-LTD, or LTP in either male or female Cd11b-/- or C3-/- mice compared to littermate controls. Knockouts showed unchanged expression level of excitatory synaptic proteins. Results and Discussion: Surprisingly, neither basal synaptic function nor changes in AMPAR trafficking during activity-dependent plasticity were dependent on the complement cascade in the hippocampus during development. Given there are complement-dependent changes in synaptic plasticity at SC synapses in AD mouse models, the mechanisms underlying these changes may not be recapitulating a developmental phenotype, as has been proposed. Future experiments will investigate the circuit-specific role of the complement cascade in hippocampal developmental pruning.

2-B-58 *Mechanisms of PTPσ-mediated presynaptic differentiation*

Claire Bomkamp[1], Nirmala Padmanabhan[2], Benyamin Karimi[2], Jesse Chao[1], Christopher Loewen[1], Tabrez Siddiqui[2], Ann Marie Craig[1]

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

Formation of synapses between neurons depends in part on binding between axonal and dendritic cell surface synaptic organizing proteins, which recruit components of the developing presynaptic and postsynaptic specializations. One of these presynaptic organizing molecules is protein tyrosine phosphatase σ (PTPσ). Although the domains involved in adhesion between PTPσ and its postsynaptic binding partners are known, the mechanisms by which it signals into the presynaptic neuron to recruit synaptic vesicles and other necessary components for regulated transmitter release are not well understood. One attractive candidate to mediate this function is liprin-α, a scaffolding protein with well-established roles at the synapse. We systematically mutated residues of the PTPσ intracellular region and used the yeast dihydrofolate reductase protein complementation assay to screen for disrupted interactions between mutant forms of PTPσ and its various binding partners. We show that disrupting the interaction between PTPσ and liprin-α, but not between PTPσ and itself or another binding partner, caskin, abolishes presynaptic differentiation. Furthermore, phosphatase activity of PTPσ and binding to extracellular heparan sulfate proteoglycans are dispensable for presynaptic induction. Previous reports have suggested that binding between PTPσ and liprin-α is mediated by the PTPσ membrane-distal phosphatase-like domain. However, we provide evidence here that both of the PTPσ phosphatase-like domains mediate binding to liprin-α and are required for PTPσ-mediated presynaptic differentiation.

2-B-59 *Effect of ATRX inactivation on hippocampal synaptic plasticity in mice*

Radu Gugustea[1], Renee Tamming[1], Stan Leung[1], Nathalie Berube[1]

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[1]The University of Western Ontario

Alpha thalassemia X-linked intellectual disability (ATR-X) syndrome is a severe cognitive disorder caused by mutations in the gene ATRX, which encodes a chromatin-remodeling protein. Mice with conditional ablation of Atrx in postnatal forebrain excitatory neurons (ATRX-KO) displayed spatial learning and memory impairments. Using electrophysiological techniques, we aimed to study major hippocampal pathways to provide insight into the spatial memory deficits observed in ATRX-KO mice. We hypothesized that hippocampal synaptic transmission and plasticity are disrupted in ATRX-KO mice. Long-term potentiation (LTP), a cellular correlate of memory, and input-output relation of paired-pulse responses were studied in urethane-anesthetized mice in vivo with a 16-channel probe following stimulation of several major hippocampal excitatory synaptic pathways. Theta-burst stimulation (TBS) of stratum oriens and medial perforant path (MPP) were used to induce LTP in the CA1 basal and distal apical dendrites, respectively. Stratum oriens TBS induced robust basal dendritic LTP in CA1 of both ATRX-KO and control mice, while paired-pulse facilitation (PPF) during baseline was lower in ATRX-KO mice compared to controls. TBS of the MPP induced CA1 distal apical dendritic LTP that was significantly decreased in ATRX-KO mice relative to control mice. LTP of the trisynaptic (MPP to CA1) response was also decreased in ATRX-KO mice compared to controls. The defects we identified in hippocampal synaptic transmission and LTP may underlie the memory impairments in ATRX-KO mice.

2-B-60 *Glutamatergic synapse maintenance, Rab10 phosphorylation, and effects of LRRK2 kinase inhibition in a VPS35 D620N knock-in mouse model of Parkinson's disease*

Chelsie Kadgien[1], Anusha Kamesh[2], Anouar Khayachi[3], Matthew Farrer[4], Austen Milnerwood[3]

[1]Montreal Neurological Institute, McGill and UBC, [2]Montreal Neurological Institute, McGill, [3]Montreal Neurological Institute, [4]UBC

VPS35 is a core component of the retromer complex, involved in endosomal recycling and surface trafficking of multiple neurotransmitter receptors including AMPAR. The D620N (DN) mutation in VPS35 is linked to late-onset, autosomal-dominant Parkinson's disease (PD) that is clinically similar to idiopathic PD. We have reported that this mutation leads to aberrant dopamine release in knock-in mice, and that exogenous expression of mutant protein alters glutamate transmission in cortical neurons. Mutations in another protein, LRRK2, are also linked to late-onset autosomal dominant Parkinson's disease, and we have reported aberrant glutamate and dopamine transmission in the G2019S knock-in mouse model PD. It has recently been reported that Rab10 is a substrate of LRRK2 and that PD-causing mutations in both LRRK2 and VPS35 significantly increase Rab10 phosphorylation. Rab10 is a small GTPase shown to play a role in GLR-1 trafficking in C. elegans. Here we explore AMPAR trafficking, protein localization, Rab10 phosphorylation, and early synaptic dysfunction in the VPS35 D620N knock-in mouse model of PD. We have uncovered alterations in dendritic localization of VPS35 and associated proteins,

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alongside increased glutamate transmission in brains and cultured cortical neurons from knock-in mice. Our evidence supports increased Rab10 phosphorylation in brain lysate from knock-in animals, which is rescued by MLi2 (a LRRK2 kinase inhibitor). We provide evidence of dendritic Rab10/pRab10 co-localization with VPS35 and GluA1 in cultured murine cortical neurons. Further, LRRK2 kinase inhibition with MLi2 has been used to uncover VPS35 and LRRK2 interactions that regulate glutamate synapse function in VPS35 knock-in and wild-type mice.

C - Disorders of the nervous system

2-C-61 *Identification of shared protein interaction networks between high-risk Autism genes through proximity-based proteomics*

Nadeem Murtaza[1], Chad Brown[1], Annie Cheng[1], Brianna Unda[1], Jarryll Uy[1], Vivian Vuong[1], Eric Deneault[2], Kanwal Singh[1], Yu Lu[1], James Ellis[3], Stephen Scherer[3], Brad Doble[1], Karun Singh[1]

[1]McMaster University, [2]University of Toronto, [3]The Hospital for Sick Children

Autism spectrum disorder (ASD) is a complex group of neurodevelopmental disorders with an exceedingly high prevalence rate (1 in 66 children in Canada). Without proper treatment these individuals are predicted to have poor long-term outcomes in education, employment, and social relationships. Unfortunately, there are no robust treatments for ASD due to the high genetic heterogeneity and incomplete research of the shared pathological pathways of ASD risk genes. Many of the known ASD risk genes fall into major cellular networks, however, studying each individual gene is inefficient and provides only partial views into the shared pathology. To identify shared interaction networks of high risk and strongly associated ASD genes we are utilizing the proximity protein-labelling technique, BioID. By identifying the protein interaction networks (PINs) of ASD risk genes in mouse cortical neurons we will elucidate whether there are any shared links between unstudied genes and functionally characterized ASD genes. Preliminary work with the ASD-associated TAOK2 gene has revealed its interaction with networks never previously identified, involving translational regulation and cellular respiration. We also validated these newly associated TAOK2 PINs, and showed that Taok2 KO mouse cortical neurons and human TAOK2 KO neurons have altered protein translation and cellular respiration. Identification of the shared ASD-linked PINs of numerous risk genes will provide a resource to advance the development of robust therapeutics and to study idiopathic cases of ASD through proteomic analysis.

2-C-62 *Decreased expression of MANF leads to motor dysfunction and alters ER stress pathways: MANF's role in Parkinson's disease pathophysiology*

Ashley Bernardo[1], Omar Shawaf[1], Khaled Nawar[1], Ram Mishra[1]

[1]McMaster University

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Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a neurotrophic factor involved in the survival and maintenance of several neuronal and other cell types, more specifically, midbrain dopaminergic neurons. MANF plays a key role in ameliorating endoplasmic reticulum (ER) stress through its activation of the unfolded protein response (UPR). Chronic ER stress that the UPR cannot overcome leads to apoptosis. The chronic ER stress induced shift to neurodegeneration is hypothesized to be one of the factors involved in dopaminergic neuronal loss in Parkinson's disease (PD). Thus far, studies have investigated the therapeutic potential of MANF in PD models, but to date limited research has specifically investigated MANF's role in PD pathophysiology. This study used lentiviral mediated shRNA particles to produce a localized MANF knockdown (KD) in the substantia nigra (SN) of rats and tested a battery of motor tests evaluating balance, gait, and coordination over 10 months. Deficits in motor function were found using narrow beam transversal, fixed speed rotarod and local asymmetry was displayed using the cylinder test and amphetamine induced rotations. RT-qPCR confirmed MANF KD and identified a significant decrease in the ER stress marker glucose regulated protein 78 (GRP78) and an increase in the apoptosis marker C/EBP homologous protein (CHOP). This study demonstrates the presence of PD like motor impairments after MANF KD in the SN and its role in ER stress related apoptosis, warranting further investigation of MANF in reference to PD pathophysiology. Supported by CIHR.

2-C-63 *The FDA-approved anti-cancer drug, nilotinib improves astroglials bioenergetics in Alzheimer's disease*

Aida Adlimoghaddam[1], Raymond Scott Turner[2], Benedict Albensi[3]

[1]St. Boniface Hospital Research Centre, [2]Neurol., Georgetown Univ., Washington, DC, [3]University of Manitoba. St. Boniface Hospital Research Centre

Alzheimer's disease (AD) is the most common form of dementia. AD is characterized by the accumulations of amyloid beta and neurofibrillary tangles in brain tissue; however, AD is multifactorial and apparently involves different etiopathogenic mechanisms that can affect mitochondrial function that are associated with AD. In the current study, we investigated the effect of nilotinib, on mitochondrial function in AD. Astroglial and neuronal cells were isolated separately from cortical brain tissue of control mice associated with the 3xTg model of AD. Oxygen consumption rate (OCR) was measured in control vs. AD cells utilizing the XF24 analyzer after a 24 hr. dose-dependent treatment with nilotinib. Western blots were used to detect expression levels of key proteins involved in mitochondrial function and memory: NF-κB subunits, pCREB, MnSOD, and mitochondrial complex protein subunits (OXPHOS) in astroglia cells in the presence/absence of nilotinib treatment. Our astroglials data show nilotinib improves ($p<0.05$) mitochondrial OCR in AD but not control. Additionally, we found nilotinib increased ($p<0.05$) expression of NF-κB p50/p105 subunits, pCREB, and MnSOD in AD cells and NF-κB p50/p105 subunits and pCREB in control cells. Moreover, nilotinib increased expression of mitochondrial

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complex (II-V) protein subunits in AD cells but not in controls. Unlike astroglials, nilotinib did not alter mitochondrial function in neuronal cells from AD or control. Overall, these results highlight a role for nilotinib in regulating bioenergetics in early stage AD and suggest that astroglial cel

2-C-64 *Excitatory and inhibitory currents underlying cross frequency coupling features during seizure-like event state transitions*

Vanessa Breton[1], Berj Bardakjian[2], Peter Carlen[1]

[1]Krembil Research Institute, [2]University of Toronto

In the neocortex, phase amplitude cross frequency coupling (CFC) between low and high frequency oscillations is a basic feature of network communication. Different frequency bands coupled with each other can indicate the interaction of different neural populations. Evidence suggests that enhanced CFC is present before and during seizures; however, the current bases for the pathological network activity has yet to be determined. Therefore, using an ex vivo brain slice preparation, low Mg2+ induced seizure-like events (SLEs) were measured in the superficial layer of the mouse neocortex. Local field potential (LFP) electrodes recorded the events. From nearby pyramidal neurons, an electrode in whole cell voltage clamp configuration recorded spontaneous synaptic excitatory and inhibitory currents. Using a feature set encompassing broad-band CFC, state distribution probabilities were computed to classify SLE onset and termination sub-states. We monitored the synaptic currents during these defined transition periods. The peaks in these currents had distinctive coupling to the phase of low frequency oscillations in the onset as compared to the termination states. Though excitatory currents peaked at variable phases of the LFP and varying low frequency bands, inhibitory currents peaked at specific phases of the 4Hz rhythm during onset, which then phase-shifted during termination. These data demonstrate the excitatory and inhibitory current bases for CFC features during SLEs.

2-C-65 *Down-regulation of the potassium chloride co-transporter KCC2 in various animal models of Alzheimer's disease*

Iason Keramidis[1], Jogender Mehla[2], Antoine Godin[1], Majid Mohajerani[2], Yves de Koninck[1]

[1]Université Laval, [2]Lethbridge University

Alzheimer disease (AD) is associated with an abnormal brain activity common to other brain disorders. A growing number of evidence suggest an imbalance between synaptic excitation and inhibition may result into an aberrant neuronal network activity underlying the behavioral deficits observed in these diseases. Such a disruption appears to occur in the pre-symptomatic phases of AD where impaired GABAergic transmission arise cortical and hippocampal seizure-like

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activity. Deficits in the potassium-chloride cotransporter KCC2, responsible for maintaining low intracellular chloride in neurons for robust inhibition, are implicated in many neurological disorders. This raises the hypothesis that KCC2 hypofunction underlies abnormal brain activity during preclinical and/or clinical phases of AD. In this end, we tested if there are any changes in KCC2 which can induce hyperexcitability but also deficits in the quality of network oscillations. A decrease in the protein levels of KCC2 in the prefrontal cortex of the 5xFAD mice was observed through immunofluorescent analysis. Specifically, the total levels of KCC2 are decreased in proximity to plaques while the membrane levels of KCC2 are lowered throughout the prefrontal cortex of the 5xFAD. Finally, our preliminary results in another animal model of AD, showed that treatment of the APPNL-G-F mice with the CLP290, an enhancer of KCC2 activity, improves the learning performance in the Morris water maze test. In conclusion, these results highlight KCC2 as a novel target for regulating the GABAergic neuronal activity in AD.

2-C-66 *Investigating the role of the high-risk Autism-associated gene SCN2A using human iPSC-derived neurons*

Elyse Rosa[1], Chad Brown[1], Sean White[1], Vickie Kwan[1], Eric Deneault[2], Biren Dave[1], Yu Lu[1], James Ellis[3], Stephen Scherer[3], Bradley Doble[1], Karun Singh[1]

[1]McMaster University, [2]University of Toronto, [3]The Hospital for Sick Children

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with impaired social communication and repetitive behaviours. Studying ASD-linked genes is necessary to understand its etiology and develop therapeutics. This project focuses on SCN2A, which encodes for sodium voltage-gated channel alpha subunit 2. Multiple recurrent and de novo mutations of SCN2A have been found in ASD probands. SCN2A regulates action potential initiation, but how its disruption leads to neurodevelopmental abnormalities is unknown. We previously reported that human isogenic iPSC-derived SCN2A knock-out (KO) neurons have decreased neuronal activity and population network activity using patch-clamp and multi-electrode array electrophysiology. We recently found using a second line of isogenic neurons that SCN2A KO and Het (+/-) neurons have decreased network activity and reduced dendrite branching and synapse formation, demonstrating haploinsufficiency of SCN2A produces a synaptic phenotype and that excitatory synaptic transmission is disrupted by loss of SCN2A function. Signaling networks mediated by SCN2A will be elucidated via RNA sequencing and proteomic analysis. Proximity-based proteomics (BioID2) will also be used to functionally annotate the changes in protein interaction networks in SCN2A KO neurons to determine how neural activity regulates synaptic signaling. Given the increasing prevalence of ASD, generating human-derived neuronal models of a disrupted high-risk ASD gene, combined with proteomic approaches, will help determine ASD-relevant therapeutic targets for drug treatment.

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2-C-67 *Striatal chloride homeostasis and inhibitory synaptic transmission is altered in huntington's disease*

Melissa Serranilla[1], Kelly Chen[1], Jessica Pressey[1], Melanie Woodin[1]

[1]University of Toronto

Huntington's disease (HD) is a neurodegenerative disorder which manifests as involuntary movements, cognitive and psychiatric perturbations. The primary pathology occurs in the brain with significant degeneration in the striatum, an area responsible for goal-directed behaviour. Recent evidence reveals that alterations in inhibitory synaptic transmission may play a critical role in the selective degeneration of the HD striatum. Synaptic inhibition in the mature brain is largely mediated through the neurotransmitter, γ-aminobutyric acid (GABA) and its activation of Cl- -permeable GABAA receptors. Fast GABAergic inhibition requires low intracellular Cl- levels ([Cl-]i), which is largely maintained by the potassium-chloride cotransporter, KCC2. A reduction in KCC2 function may lead to increased [Cl-]i and impaired synaptic inhibition. This study aims to determine whether KCC2 is compromised in the HD striatal circuitry. Biochemistry, electrophysiology and behavioural assays were used to determine alterations in KCC2 function in two mouse models of HD, the R6/2 and YAC128 mice. In symptomatic mice, striatal KCC2 protein expression was reduced and a depolarization of the reversal potential for GABA was observed, indicating a reduction in Cl- extrusion capacity. The remainder of this study will examine how rescuing striatal KCC2 function may ameliorate the symptoms of HD. This work may provide evidence that impairments in GABAergic inhibition may be a key mechanism underlying circuitry defects, whereby KCC2 may serve as a potential therapeutic target in the treatment of HD.

2-C-68 *Computational modelling indicates irregularity in alpha-helical angular orientation among aggregatory Parkinsonian variants of α-synuclein*

Alexander Ille[1], Hannah Lamont[1], Jeremiah Davie[1], Stacy Ruvio[1], Mathias Moise[2], Stacy Ruvio[1], Raoul Bodea[3]

[1]D'Youville College, [2]University of Waterloo, [3]STEM Biomedical

Parkinson's disease (PD) is among the most common neurodegenerative disorders causing cognitive impairment. Abnormal aggregation of α-Synuclein in various brain regions is a pathological hallmark in PD with cognitive impairment. α-Synuclein is a 140-residue protein which exists physiologically as a helically folded tetramer that resists aggregation. The alpha-helical region of α-synuclein is considered important in the context of neurotoxicity, autophagy, and aggregation. Here we employed computational modelling to identify variation between wildtype α-synuclein and Parkinsonian variants of α-Synuclein. The Parkinsonian variants analyzed include A53E, A53T, and A53V, which have all been documented to occur in familial PD with cognitive impairment. Methods used for computational modelling include both homology-based and ab

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initio structural prediction. Our results reveal irregularity in alpha-helix angular orientation among these mutant variants and wildtype α-Synuclein. Additionally, the variations in angular orientation observed correspond with the aggregation propensities of α-synuclein variants as demonstrated in recent research. These data provide further insight into the molecular aspects involved in neurodegenerative synucleinopathy.

2-C-69 *Expression of Na+/K+-ATPase isoforms in higher and lower brain regions following focal ischemia in mice*

Chloe Lowry[1], Brian Bennett[1], R. David Andrew[1]

[1]Queen's University

Clinically and experimentally, higher gray matter is more susceptible to acute ischemic injury than lower gray matter. Discovering the mechanisms which contribute to the brainstem's resilience may inform targets for improved survival of higher brain neurons. As failure of the Na+/K+-ATPase is a key event following ischemia, we hypothesize that differential regional susceptibility of the brain to ischemia might be explained in part by variable expression of Na+/K+-ATPase isoforms, which differ in pumping efficiency under low energy conditions. Our previous mRNA expression analyses in mice have shown that under basal conditions, the ischemia-vulnerable alpha1 isoform is on average 2.2x higher than alpha3 in neocortex, whereas the ischemia-resistant alpha3 isoform is on average 2x higher than alpha1 in brainstem. Parallel protein expression analyses are consistent with these findings. Preliminary data from mice undergoing a 30-minute middle cerebral artery occlusion (MCAo) shows that 24-hours post-stroke, mRNA expression of alpha1 decreases significantly in the ischemic compared to control hemisphere. We are currently following up these results with analysis of alpha1 and alpha3 mRNA and protein levels in various higher and lower brain regions of mice undergoing MCAo. We suspect alpha1 expression will decrease and alpha3 will increase following stroke, particularly in the neocortex. Understanding how Na+/K+-ATPase isoforms may differ in their expression in response to metabolic stress will yield insights into how such differences protect neurons during ischemia.

2-C-70 *Aging mice show motor deterioration and Purkinje cell firing alterations*

Eviatar Fields[1], Alanna Watt[1]

[1]McGill University

Canada is facing a growing "aging epidemic" arising from the economic burden of an aging population. Declines in motor coordination, impaired gait, and balance deficits are common changes that accompany aging and limit a person's quality of life and independence. The

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cerebellum is critically involved in motor coordination and gait, and its Purkinje cells fire spontaneous action potentials at high frequencies which is disrupted in mouse models of ataxia. Interventions that rescue Purkinje cell firing rate deficits have been shown to improve motor coordination in ataxic models suggesting that high frequency firing is important for normal cerebellar function, yet little is known about Purkinje cell firing properties in aged animals to date. We wondered whether healthy aging mice might share similar cerebellar alterations as ataxic mice. To address this, we studied motor coordination and gait in healthy C57Bl/6J mice at several ages from young to old adult. We then performed loose cell-attached recordings of Purkinje cell action potentials in acute cerebellar slices at these time points. We found that motor coordination declined with age, and that this was accompanied by an age-dependent reduction in Purkinje cell firing rates that was reminiscent of the changes observed in ataxia models. These findings suggest that cerebellar-related motor decline observed in healthy aging and in ataxia may share similar pathophysiology. Our current experiments focus on rescuing the reduced rates of firing in aged Purkinje cells with the goal of restoring motor coordination in aged mice.

2-C-71 *Role of IL-1beta in inflammation-mediated disruption of neural circuit development*

Cynthia Solek[1], Nasr A Farooqi[2], Philip Kesner[2], Jack Antel[3], Edward Ruthazer[4]

[1]Montreal Neurological Institute and Hospital, McGill Universityr, [2]Montreal Neurological Institute and Hospital, McGill University, [3]Montreal Neurological Institute, [4]McGill University

Neuroinflammation initiated by maternal infection during fetal development has been strongly implicated in the etiology of neurodevelopmental disorders, including autism spectrum disorders and schizophrenia. We show that a brief exposure of Danio rerio (zebrafish) larvae with lipopolysaccharide (LPS) causes an increase in retinal ganglion cell (RGC) branching dynamics immediately after the inflammatory insult. We also saw an increase in overall size and branch number in LPS treated animals over the following several days. mRNA levels of the pro-inflammatory cytokine IL-1ß are significantly increased following LPS treatment, and morpholino oligonucleotide (MO) knock-down of this cytokine negates the immediate and long-term effects of LPS treatment. Delay of specification of the myeloid lineage, which includes microglia, by MO knockdown of the PU.1 transcription factor, eliminates the immediate effects on RGC branching dynamics, indicating a role for microglia in the mechanisms that mediate inflammation-induced neuronal defects. However, the size and complexity of the arbors several days following LPS treatment in PU.1 MO injected larvae are not significantly different than control MO animals. This suggests that microglia are involved in mediating some of the effects of LPS treatment on cellular dynamics. Zebrafish larvae can be genetically manipulated in large numbers, permitting rapid candidate signal screening in vivo. Our findings will inform translational studies that can help us better understand and potentially decrease the occurrence of neurodevelopmental disorders.

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2-C-72 *Inferring white matter structure from correlations in neural population activity*

Rabiya Noori[1], Jeremie Lefebvre[2]

[1]University of Toronto, [2]Krembil Research Institute, University Health Network

White matter (WM) plasticity plays an integral role in maintaining synchrony of brain network components by regulating conduction velocity in the propagation of neural signals. To explore the role of WM, we developed a brain-scale network model to simulate and isolate the effect of myelin structure on synchronization patterns in the human brain. This model is built of interacting oscillatory nodes, each representing an individual brain region, and described by a system of first-order nonlinear stochastic delay differential equations. Given population dynamics data for regions across the whole brain, we can optimize our model to find the set of parameters that will give rise to the given target dynamics. We have applied this approach to estimate network weights and also isolate conduction velocities along myelin tracts in our model, to get an indirect measure of myelination. We are using our approach on real MEG measurements from two cohorts: healthy vs patients with WM degradation, and are expecting to see a significant difference in how the distribution of signal delays across the brain networks differ. We also examined how robust our results were as a function of the oscillation frequency of the neural populations involved. By learning network structure using neural dynamics data we will be able to leverage our knowledge of the biophysical representation of the parameters and structure of the model, to get insight on the role of myelin in brain dynamics. Our approach will improve our understanding of disorders that affect WM plasticity, such as multiple sclerosis.

2-C-73 *Lewy pathology in the REM sleep circuit triggers REM sleep behavior disorder in mice*

Russell Luke[1], Jimmy Fraigne[1], Andrea Bevan[1], John Peever[1]

[1]University of Toronto

REM sleep behaviour disorder (RBD) is a neurological condition caused by loss of REM sleep atonia, which results in violent dream enactment during REM sleep. The most clinically concerning aspect of RBD is that 80-90% of patients eventually develop a synucleopathic neurodegenerative disease. Here, we test the longstanding but untested hypothesis that Lewy pathology in the REM sleep atonia circuit will induce RBD in mice. We used an AAV-mediated approach to over-express human alpha-synuclein in the ventral medulla (vM) of wild-type mice, which is at the core of the REM sleep atonia circuit. 10-12 weeks later we assessed if this intervention 1) induced Lewy pathology in these cells; and 2) affected motor activity during REM sleep. Sleep-wake behaviours and motor activity were assessed by EEG and EMG recordings and video monitoring. First, we

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revealed using immunohistochemical analysis that the viral delivery of alpha-synuclein caused Lewy pathology in vM cells. This was characterized by an accumulation of phosphorylated alpha-synuclein aggregates in vM cells. Second, we found that Lewy pathology in vM cells increased phasic motor activity during REM sleep (t-test; n=8, p=0.011), but more importantly it prevented REM sleep atonia (t-test; n=8; p=0.013). Third, we found that Lewy pathology in vM cells had no significant effect on overall amounts of sleep or wakefulness (t-test; n=8; p>0.05). Our findings show that Lewy pathology in the REM sleep atonia circuit triggers RBD in mice, which suggests that RBD in human patients could result from a synucleopathic mechanism.

2-C-74 *Assessing the role of amyloid precursor protein phosphorylation by polo-like kinase 2 in Alzheimer's disease*

Laura Martínez-Drudis[1], Razan Sheta[1], Laurence Labbé[1], Abid Oueslati[1]

[1]Université Laval & CHU de Québec Research Center, Neuroscience Axis

Alzheimer's disease (AD) is the major cause of dementia in the aged population, and is characterized by the accumulation of proteinaceous aggregates: amyloid plaques, composed of amyloid beta (Aβ) deposits that result from amyloid precursor protein (APP) cleavage. In vitro and in vivo evidence suggest that abnormal phosphorylation of APP plays a role in APP processing, and subsequent Aβ formation and aggregation. Our laboratory has reported a dramatic accumulation of Polo-like kinases (PLKs), notably PLK2, in the brains of AD patients. This observation, in addition to recent reports of a direct interaction between PLK2 and APP, suggests that aberrant accumulation and activity of PLK2 may contribute to AD pathogenesis. Our objective is to study the role of PLK2 in APP aggregation and neurotoxicity, and its implications in AD initiation and progression. Using immunohistology, we assessed PLK2 expression in amyloid plaques of AD transgenic mouse models (APPswe/PS1 and 3xTg-AD). Analysis of brain slices by confocal microscopy, showed perfect co-localization of PLK2 within Aβ-positive plaques in the hippocampus and cortex. We also evaluated the impact of PLK2 on APP levels in a cell-based assay, using HEK293T cells transfected with APP and PLK2. We observed that overexpression of PLK2 decreases APP levels in a PLK2-concentration dependent manner, counteracted by pharmacological inhibition of PLK2. Our results suggest that PLK2 activity modulates APP processing and may affect its accumulation in vivo, offering a new therapeutic strategy for treatment of AD and related dementia.

2-C-75 *Changes in neurite orientation dispersion and density following mild traumatic brain injury in mice*

Tong Wang[1], Lisa Gazdzinski[1], Miranda Mellerup[1], John Sled[1], Brian Nieman[1], Anne Wheeler[1]

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[1]The Hospital for Sick Children

Diffuse axonal damage following mild traumatic brain injury (mTBI) is difficult to detect by current clinical MRI protocols. Biophysical MRI models with the ability to detect microstructural changes following mTBI may provide more accurate diagnostic and prognostic information. Controlled impacts to the skull were delivered to 8-week old male mice to induce mTBI. Ex vivo multi-shell diffusion MRI (b-values=2078,5073,7305 mm/s^2) was acquired 1 and 6 weeks following impact (N=9 in each mTBI group). Sham surgical control groups, receiving no impact, were also scanned at 1 and 6 weeks (N=9 in each sham group). Image processing was performed using Neurite Orientation Dispersion and Density Imaging (NODDI) to compute the orientation dispersion index (ODI) and intracellular volume fraction (ICVF), an index of neurite density, for each image. Voxel-by-voxel comparisons revealed unilateral ODI decreases in regions of the striatum and hippocampus at 1 week in mTBI mice relative to shams, as well as ODI increases throughout the thalamus at 6 weeks relative to 1 week in mTBI mice ($p<0.05$). At 6 weeks, ODI was significantly increased bilaterally in the optic tract in mTBI mice relative to shams (FDR-corrected $p<0.05$). Bilateral ICVF increases were detected at 6 weeks relative to 1 week throughout the thalamus as well as along the corpus callosum in mTBI mice ($p<0.05$) but not shams. NODDI may be able to detect focused and diffuse changes in neurite organization with greater specificity than conventional diffusion tensor imaging, and is a potential imaging biomarker for mTBI.

2-C-76 *Characterization of somatic mutations in mTOR pathway genes in focal cortical dysplasias*

Eric Krochmalnek[1], Andrea Accogli[2], Judith St-Onge[1], Nassima Addour[1], Roy Dudley[3], Ken Myers[2], François Dubeau[3], Jason Karamchandani[2], Jean-Pierre Farmer[3], Jeffrey Atkinson[3], Jeffrey Hall[3], Chantal Poulin[2], Bernard Rosenblatt[2], Joël Lafond Lapalme[1], Steff

[1]The McGill University Health Centre Research Institute, [2]McGill University, [3]Montreal Neurological Institute and Hospital

BACKGROUND: Focal cortical dysplasias (FCDs) are congenital structural abnormalities of the brain, and represent the most common cause of medication-resistant focal epilepsy in children and adults. Recent studies have shown that somatic mutations (i.e. mutations that arise in the embryo) in mTOR pathway genes underlie some FCD cases. Specific therapies targeting the mTOR pathway are presently available, allowing for potential personalized treatment. However, testing for somatic mTOR pathway mutations in FCD tissue is not performed on a clinical basis, and the contribution of such mutations to the pathogenesis of FCD remains unknown. AIM: To investigate the feasibility of screening for somatic mutations in FCD tissue and determine the proportion of FCDs which are due to low-level somatic mTOR pathway mutations. Furthermore, we will determine the spatial distribution of these mutations throughout resected FCD tissues. METHODS: We have performed ultra-deep sequencing of 13 mTOR pathway genes using a

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custom HaloPlexHS target enrichment kit (Agilent Technologies) in 16 resected histologically-confirmed FCD specimens. RESULTS: We identified causal variants in 62.5% (10/16) of patients at an alternate allele frequency of 0.75 to 33.7%. The spatial mutation frequency correlated with the size and severity of the FCD lesions. CONCLUSIONS: Screening FCD tissue using a custom panel results in a high yield and should be considered clinically given the important potential implications regarding surgical resection, medical management and genetic counselling.

2-C-77 *Bistability as an underpinning of seizure initiation in simulated inhibitory networks*

Scott Rich[1], Homeira Chameh[1], Marjan Rafiee[1], Katie Ferguson[1], Frances Skinner[1], Taufik Valiante[2]

[1]Krembil Research Institute, [2]Krembil research Institute, University Health Network

Recent experimental literature provides evidence that synchronous activation of GABAergic interneurons may serve a causal role in seizure initiation. These observations are counterintuitive considering the common hypothesis that the seizure state involves overactivity of excitatory neurons. Given the novel nature of this hypothesis there remain crucial questions as to how the dynamical changes accompanying GABAergic seizure initiation might occur. Computational neuroscience is uniquely poised to answer such questions regarding neural dynamics; thus, tools from this field are applied here to propose a mechanism explaining the sudden transition of a hyper-excitable inhibitory network into a synchronous state that might precipitate seizure onset. We accordingly compared the dynamics of purely inhibitory networks modeled with either control or 4-Aminopyridine (4-AP - an agent that induces seizure in vivo and in vitro) treated neurons. Simulations revealed that 4-AP networks are more prone to transitions between asynchronous and synchronous firing caused by a brief perturbation to the system. Such a transition arose due to the system's predisposition towards bistability. More physiologically-grounded perturbations modeled via noise-like synaptic input were also able to drive such transitions. This result provides a convincing potential mechanism underlying the abrupt transition of inhibitory networks into synchrony in a pathological, hyper-excitable setting. In turn, our work provides a crucial piece of in silico support for the hypothesis of GABAergic seizure initiation.

2-C-78 *Expression of IGF-1 and IGF-1 receptor in human idiopathic autism*

Milena Cioana[1], Bernadeta Michalski[1], Margaret Fahnestock[1]

[1]McMaster University

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Autism Spectrum Disorder (ASD) is believed to stem from defects in the establishment and maintenance of functional neuronal networks due to synaptic/spine dysfunction. The potent effects of IGF-1 on synaptic function, maintenance and plasticity make it a potential target for treating ASD. This polypeptide hormone has proven to have beneficial effects in treating other developmental disorders like Rett Syndrome, and its efficacy in ASD is currently being tested in a pilot treatment study. IGF-1 binds to its receptor (IGF-1R) in neurons and activates mitogen-activated protein kinase (MAPK) and PI3K/Akt signaling to produce biological effects on spine function. The PI3K/Akt pathway is down-regulated in idiopathic autism and is thus believed to play a role in the disorder. Although an imbalance in BDNF and TrkB protein isoforms, which activate the PI3K/Akt pathway, has been shown in human idiopathic autism, it is possible that the pathway is also mediated by IGF-1 and its receptor. The present study explored whether IGF-1 and IGF-1R are down-regulated in human idiopathic autism. RNA and protein were extracted from post-mortem human fusiform gyrus tissue of normal controls and subjects with idiopathic autism, and qRT-PCR, ELISA and Western blots were performed. There were no significant differences between idiopathic autism and control groups, suggesting that although IGF-1 may be useful for ASD treatment, IGF-1 and IGF-1R are not implicated in the pathogenesis of idiopathic autism.

2-C-79 *Novel brain-behaviour similarity subgroups across neurodevelopmental disorders*

Grace Jacobs[1], Aristotle Voineskos[2], Natalie Forde[3], Erin Dickie[2], Meng-Chuan Lai[1], Peter Szatmari[1], Russell Schachar[1], Jennifer Crosbie[1], Paul Arnold[1], Margot Taylor[1], Anna Goldenberg[1], Lauren Erdman[1], Jason Lerch[1], Evdokia Anagnostou[1], Stephanie Ameis[1]

[1]University of Toronto, [2]Centre for Addiction and Mental Health, [3]Centre for Addition and Mental Health

Neurodevelopmental disorders (NDDs) such as autism spectrum disorder (ASD), obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD) are heterogeneous conditions with significant overlap in behaviours and brain alterations. We used Similarity Network Fusion (SNF), a multi-data integrative clustering tool, to identify novel groups across NDDs featuring more homogeneous brain-behaviour profiles than exist in DSM diagnoses. Measures from T1-weighted (cortical thickness, subcortical volume) and diffusion-weighted (fractional anisotropy) magnetic resonance imaging, and behavioural scores, were obtained for 182 children, aged 6-16 years with ASD (n=91), ADHD (n=52) or OCD (n=39) from the Province of Ontario Neurodevelopmental Disorders Network. Data integration and spectral clustering were done using SNF. General adaptive functioning measures (not involved in cluster determination) were used to evaluate validity of the identified groups. Four groups with distinct brain-behaviour profiles that cut across diagnoses were identified. Group formation and top contributing measures driving formation were shown to be stable with resampling. General adaptive functioning

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(F=21.46, p<0.0001, η2=0.28) was significantly different between groups, as were top contributing neurobiological features: right insula thickness (F=47.76, p<0.0001, η2=0.44) and right thalamic volume (F=18.51, p<0.0001, η2=0.24). Stability across other samples and clinical validity testing of these groups is needed to determine potential utility for diagnostic and treatment innovation

2-C-80 *Mitochondria transport deficits and reduced expression of mitochondrial trafficking proteins in retinal ganglion cells*

Heberto Quintero[1], Nicolas Belforte[2], Adriana Di Polo[1]

[1]University of Montreal Hospital Research Center, [2]Université de Montreal

Deficits in mitochondria trafficking along neurons have been linked to the onset of age-related neurodegenerative diseases. Glaucoma is a disease characterized by ocular hypertension (OHT), progressive death of retinal ganglion cells (RGCs) and vision loss. To investigate the role of mitochondria transport in glaucoma, we used transgenic mice carrying a mitochondrial-targeted reporter sparsely expressed in RGCs. Mitochondria transport along RGC axons was analyzed after OHT using 2-photon intravital imaging. Our data show that both anterograde and retrograde mitochondria transport along RGC axons was dramatically reduced in early stages after OHT. To identify molecular mechanisms underlying mitochondria transport deficits, we analyzed the expression levels of the trafficking adaptor proteins DISC1 and MIRO1. We found that non-injured retinas contain high levels of DISC1 in the INP and GC layers, where RGC dendrites and soma are located, respectively, whereas expression levels were markedly reduced in glaucomatous retinas. Lastly, we found that siRNA-mediated silencing of DISC1 promoted RGC death, while AAV-mediated DISC1 overexpression promoted survival, suggesting a key role of mitochondria transport in the maintenance of viable neurons in glaucoma. In summary, our data show that insults to the optic nerve result in rapid loss of mitochondria traffic along RGC processes correlating with loss of function of mitochondrial trafficking proteins. A better understanding of mitochondria transport deficits might provide new insights into strategies to prevent RGC death in glaucoma.

2-C-81 *Rostromedial tegmental activation in a preclinical model of depression-addiction comorbidity*

Tristian Critch[1], Bradley Furlong[1], Nageeb Hasan[1], Shannon Waye[1], Josh Conway[1], Francis Bambico[1]

[1]Memorial University of Newfoundland

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High comorbidity between depression and addiction often impedes successful treatment. We examined comorbidity-like states in rodents by combining the olfactory bulbectomy (OBX) model of depression with a two-bottle, free-choice ethanol consumption test. OBX displayed increased locomotor activity and ethanol consumption, indicative of a comorbid symptom profile. We then tested the response of the rostromedial tegmental nucleus (RMTg) to ethanol since it is known to mediate the impact of aversive stimuli on dopamine and serotonin activity, which are implicated in addiction and depression, respectively. Biosensor glucose utilization measurements showed divergent acute (30 min post-injection) and subacute (>30 min post-injection) activational responses of the RMTg to ethanol between OBX and sham. For acute effects, the glucose signal maintained a biphasic negative-positive profile for 30 mins. Sham animals displayed lower peak-trough amplitudes, suggesting lower acute RMTg reactivity to ethanol. For subacute effects, OBX animals displayed a prolonged (4 hrs) decrease in signal, suggesting a stable decrease in basal RMTg activity. Moreover, OBX powerfully attenuated the correlational strength between RMTg activation and comorbidity scores, indicating a narrowing of the dynamic range in RMTg activation. These findings that differences in comorbidities were associated with alterations in RMTg response suggests that the RMTg may serve to mediate increased concurrence of symptoms, and potentially offers a biomarker or therapeutic target to effectively treat these comorbid disorders

2-C-82 *Antidepressant effects of transcranial direct current stimulation (tDCS) and adjunct paroxetine treatment in adolescent rats*

Shannon Waye[1], Francis Bambico[1]

[1]Memorial University of Newfoundland

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that sends weak electrical current through the skull, resulting in neuroplastic changes. Although its therapeutic effects have been documented in treating depressive disorders in adults, no such studies have been conducted using adolescent subjects. We induced a depressive-like phenotype in adolescent Sprague-Dawley rats using olfactory bulbectomy (OBX), a rodent model of depression that results in behavioural and neurochemical changes that are reversed by antidepressant treatment. We examined if two weeks of tDCS treatment resulted in reductions of OBX-induced depressive-like behavioural symptoms, including hyperlocomotion in an open field chamber, immobility in a forced swim test, and deceased sucrose consumption, and if this effect was achievable with tDCS alone or with adjunct Paroxetine treatment. Finally, we examined whether the antidepressant-like activity of tDCS is linked to its capacity to reverse stress hormone overproduction and increase the growth-stimulating protein BDNF by collecting blood and extracting brain tissue for ELISA analysis. Based on previous work in our lab, we expect that both OBX surgery and chronic Paroxetine treatment will increase depressive-like symptoms in adolescent rats, and that tDCS will reverse these effects.

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2-C-83 *Insulin growth factor-1, unlike insulin, does not promote retinal ganglion cell dendrite regeneration after axonal injury*

Sara Vucetic[1], Jessica Agostinone[1], Adriana Di Polo[2]

[1]University of Montreal, [2]University of Montreal Hospital Research Center

Glaucoma is the leading cause of irreversible blindness worldwide. Loss of vision in glaucoma results from the death of retinal ganglion cells (RGCs), neurons that convey information from the retina to the brain. A challenge in the management of glaucoma is that pathological changes in these patients occur years before symptoms appear. Thus, there is an unmet need for therapies that stimulate RGC regeneration and restore vision. One of the earliest signs of damage in glaucoma is the retraction of RGC dendrites, the fine processes that connect neurons. Recently, we showed that human recombinant insulin, administered after dendritic shrinkage, promoted dendritic and synaptic regeneration, restoration of RGC function, and increased cell-survival. The goal of this study was to verify whether insulin-like growth factor 1 (IGF1), an insulin-mimetic, promotes RGC dendritic regeneration. For this purpose, Thy1-YFP mice were subjected to optic nerve axotomy to induce RGC dendritic retraction. IGF1 was injected intravitreally at 3 days and its regenerative potential was characterized at 7 days post-axotomy by detailed 3D analysis of dendritic morphology. RGC survival was assessed by immunohistochemistry on flat-mounted retinas. Our data show that IGF1 did not promote significant dendritic regeneration and survival using different concentrations. Our results support the surprising conclusion that IGF1 does not have a similar pro-regenerative capacity as insulin and suggest limitations at the level of IGF1 receptor signaling or downstream components in eliciting dendrite regeneration.

2-C-84 *The retrograde transport of BDNF and proNGF diminishes with age in basal forebrain cholinergic neurons*

Arman Shekari[1], Margaret Fahnestock[1]

[1]McMaster University

Profound and early basal forebrain cholinergic neuron (BFCN) degeneration is a hallmark of Alzheimer's disease (AD). BFCNs depend for survival and function on neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) which are retrogradely transported from BFCN target tissues. In AD, NGF-immunoreactive material is found at abnormally high levels in BFCN targets like cortex and hippocampus and is reduced in basal forebrain, suggesting dysfunctional retrograde axonal transport of neurotrophins. Age is the greatest risk factor for developing AD, yet the influence of age on BFCN axonal transport is poorly understood. To model aging, E18 rat basal forebrain or cortical neurons were cultured in microfluidic chambers

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for 3 weeks. Neurons were assayed after either 7 or 18 days in vitro. To confirm an aging phenotype, cells were stained for senescence-associated beta-galactosidase (SaβG) at both time points. Quantum dot-labeled BDNF or proNGF were added to the axon terminals. DIV7 BFCNs displayed robust BDNF and proNGF transport, which diminished with in vitro age. BDNF transport did not diminish with age in cortical neurons. Significant SaβG staining was observed in aged BFCNs but not in cortical neurons cultured for 18 or more days in vitro. These results strongly suggest a vulnerability of BFCNs to age-induced retrograde transport deficits. BFCNs' unique susceptibility to age-induced retrograde axonal transport impairments, coupled with their reliance on neurotrophin transport, may explain their vulnerability to age-related disorders like AD.

2-C-85 *Amyloid toxicity or chronic cerebral hypoperfusion on the brain insulin resistance in a rat model with intracerebroventricular streptozotocin*

Hahn Young Kim[1], Bo-Ryoung Choi[1], Ju Ha Seo[1], Dong Bin Back[1]

[1]Konkuk University Hospital

Background Sporadic Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder affected by amyloid or vascular pathogenesis. Brain insulin resistance (BIR) has been has been suggested as one of pathomechanism of sporadic AD. We investigated how amyloid or vascular pathogenesis of AD works on the BIR. Methods We designed experimental groups mimicking amyloid pathogenesis by intracerebroventriculr (icv) injection of amyloid β and vascular pathogenesis by permanent ligation of bilateral common carotid arteries in Wistar rats with streptozotocin (STZ)-icv injection. Behavioral tests and pathologic studies were performed. Results Cognitive impairments, neuroinflammation, AD-related, and tau-related pathology was induced by BIR. Pathologic response was different depending on the amyloid or vascular pathogenesis and sometimes synergistically aggravated when BIR is combined. Sensitivity to the amyloid or vascular pathogenesis may be different depending on brain regions such as white matter or hippocampus. Conclusion Our study may provide useful experimental insights based on the integrated approach with amyloid and vascular pathogenesis on the BIR to understand the heterogeneous pathogenesis of sporadic AD.

2-C-86 *The dynamics of TAR DNA-binding protein 43 in stress granules and its role in amyotrophic lateral sclerosis*

Ashley Bo Zhang[1], Shangxi Xiao[1], Philip McGoldrick[1], Janice Robertson[1]

[1]University of Toronto

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Amyotrophic lateral sclerosis (ALS) is characterized by the degeneration of upper and lower motor neurons, and is pathologically typified by cytoplasmic inclusions containing TAR DNA-binding protein 43 (TDP-43) in degenerating neurons. TDP-43 is a DNA/RNA binding protein that is recruited to stress granules. Stress granules triage translationally stalled pre-initiation complexes, promoting expression of mRNAs necessary for cell survival. TDP-43 is abnormally phosphorylated in ALS, and the role of this abnormal phosphorylation in stress granule dynamics has not been widely explored. We hypothesize that TDP-43 phosphorylation is important for stress granule dynamics and that this event is dependent on cell type and stressor. HEK293, SH-SY5Y, and HeLa cells were stressed with sodium arsenite, hydrogen peroxide, and sorbitol and allowed to recover before assessing stress granule formation and TDP-43 localization. Sodium arsenite induced stress granule formation after 1h, detected using an antibody to G3BP1. However, the dynamics of TDP-43 recruitment to stress granules were much slower, occurring only in HeLa cells after 24h recovery from sodium arsenite. Importantly, TDP-43 recruitment to stress granules correlated with phosphorylated TDP-43. Our results demonstrate that recruitment of TDP-43 to stress granules is context-specific, depending on both cell type and nature of the stressor. Further investigation into the effects of TDP-43 phosphorylation in stress granule dynamics may provide new insight into the interplay between TDP-43 and stress granules in ALS pathogenesis.

2-C-87 *The prion protein is embedded in a molecular environment that modulates transforming growth factor β and integrin signaling*

Farinaz Ghodrati[1], Mohadeseh Mehrabian[1], Declan Williams[1], Ondrej Halgas[1], Matthew E. C. Bourkas[1], Joel C. Watts[1], Emil F. Pai[1], Gerold Schmitt-Ulms[1]

[1]University of Toronto

At times, it can be difficult to discern if a lack of overlap in reported interactions for a protein-of-interest reflects differences in methodology or biology. A case in point is the prion protein (PrP), best known for its central role in prion disorders. In such instances, systematic analyses of protein-protein networks across diverse paradigms can provide valuable insights. Here, we interrogated the PrP interactome in four mouse cell lines. Analyses made use of identical affinity capture and sample processing workflows. Negative controls were generated from PrP knockout lines of the respective cell models, and the relative levels of peptides were quantified with the help of isobaric labels. The study uncovered 26 proteins, which reside in proximity to PrP. All of these proteins are predicted to have access to the outer face of the plasma membrane, and approximately half of them were not reported to interact with PrP before. Strikingly, although several proteins exhibited profound co-enrichment with PrP in a given model, except for Neural Cell Adhesion Molecule 1 (NCAM1), no protein was highly enriched in all four PrP-specific interactomes. A majority of proteins that co-purified with PrP are known to play roles in epithelial-to-mesenchymal transition (EMT), either by acting as transforming growth factor β (TGF-β) signaling modulators,

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through facilitating the formation of NCAM1-dependent focal adhesion complexes, or by mediating integrin-mediated downstream cell signaling.

2-C-88 *Neuroprotective effect of sigma-1 receptor on synaptic function & calcium handling in Huntington disease*

Wissam Nassrallah[1], James Mackay[1], Amy Smith-Dijak[1], Lynn Raymond[1]

[1]University of British Columbia

Huntington disease (HD) is a monogenic disorder with autosomal dominant inheritance. In HD patients, neurons involved in motor function degenerate leading to motor and cognitive problems. Dysregulation of synaptic function and Ca2+ handling is a common trait of many neurodegenerative disorders such as Parkinson's, Alzheimer's, and HD. One level of Ca2+ regulation is at the endoplasmic reticulum (ER). This Ca2+ regulation is abnormal in HD. The ER has also been shown to be involved in synapse-to-nuclear communication, and I hypothesize that this mechanism is altered in HD. Sigma-1 Receptors (S1Rs) are proteins located on the ER that play an important role in Ca2+ regulation and thus gene transcription. Interestingly, activating S1Rs has been shown to normalize this Ca2+ handling and 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, and synaptic function, to better understand the pathophysiological mechanisms of HD and to find new potential treatments. Using electrophysiology, pharmacology, and the YAC128 HD mouse model, our data shows that elements of synaptic dysfunction, such as impaired homeostatic synaptic plasticity, in YAC128 cortical cultures are rescued by a S1R agonist. Ca2+ imaging also suggests impairments in nuclear signaling in YAC128 spiny projection neurons in corticostriatal co-cultures. This project will help us understand the complex pathogenesis of HD and elucidate the roles of key therapeutic targets, toward developing disease-modifying treatments.

2-C-89 *Attenuation of cytotoxic edema by minocycline*

Anne-Sophie Sack[1], John Tyson[1], Hyun Choi[1], Nicholas Weilinger[1], Brian MacVicar[1], Terrance Snutch[1]

[1]University of British Columbia

Acute brain injury can lead to cerebral edema, an abnormal accumulation of water mediated by cytotoxic, ionic and vasogenic edema. Cytotoxic edema, a subclassification of cerebral edema involving cellular swelling, triggers signaling cascades leading to cellular death in addition to supplying a driving force for brain swelling. Minocycline, a tetracycline antibiotic that readily

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crosses the blood brain barrier, has been established to exhibit neuroprotective properties. These effects have been attributed to anti-inflammatory, anti-apoptotic and anti-oxidative effects. Interestingly, this antibiotic has also been shown to reduce cerebral edema in various injury models. However, these effects have focused on the final components of cerebral edema and the underlying cellular mechanism remains to be described. Here, utilizing rat hippocampal slices in a novel ex vivo veratridine-triggered swelling assay, we find that minocycline reduces both the rate of swelling and the overall degree of swelling. Compared to controls, the decreased swelling by minocycline is further accompanied by an inhibition of cell death measured by lactate dehydrogenase release. Ongoing work includes examining the cellular basis of minocycline-mediated attenuation of brain slice swelling using 2-photon imaging as well as the in vivo applications of this effect.

2-C-90 *Investigation of the role of MATR3 in cryptic splicing*

Xiao Xiao (Lily) Chen[1], Hari Krishna Yalamanchili[2], Rebekah van Bruggen[3], Zhandong Liu[4], Jeehye Park[5]

[1]University of Toronto, Sickkids Research Institute, [2]Baylor College of Medicine, [3]University of Toronto, [4]Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, [5]The Hospital for Sick Children

RNA splicing plays a critical role in neuronal development, but we lack a thorough understanding of the function of each RNA binding protein (RBP) and the molecular mechanism by which these RBPs regulate splicing in neurons. MATR3 is an RBP associated with a neurodegenerative disease and it is highly expressed in the nervous system, which suggests that MATR3 plays important roles in neurons. Recent studies suggest that MATR3 acts as a splicing repressor of alternative exons and LINE-derived exons which include novel and unannotated exons called "cryptic exons". We hypothesize that MATR3 regulates cryptic splicing (CS) which involves splicing of cryptic exons in the genome. To test this, we knocked down MATR3 in HeLa cells using siRNA. The total RNA was paired end sequenced resulting in 100 million paired end reads. Reads were aligned to the human genome and analyzed for RNA splicing events. Upon MATR3 knockdown, we identified 3,235 alternative splicing events and 557 CS events. We were able to validate several of the CS events found upon MATR3 knockdown in the SH-SY5Y cell line that has neuronal characteristics. Currently we are exploring which protein domains of MATR3 are required for CS and planning to perform RNA sequencing experiments in SH-SY5Y cells with MATR3 knocked down. To examine MATR3 dependent regulation of CS, we will determine if transcripts that undergo CS contain MATR3 binding sites. This study will be able to determine the splicing events and transcripts regulated by MATR3 and the molecular mechanism of MATR3 mediated splicing.

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2-C-91 *Variations in the expression of a gene network coexpressed with syntaxyn1a in rodents interacts with early life trauma in determining susceptibility/resilience to depression in humans*

Carla Dalmaz[1], Irina Pokhvisneva[2], Ana Toniazzo[1], Danusa Arcego[2], Kieran O'Donnell[2], Michael Meaney[2], Patricia Silveira[2]

[1]Universidade Federal do Rio Grande do Sul, [2]McGill University

Gene x environment interactions have been considered in the development of depressive disorders. Changes in neuroplasticity and specific synaptic proteins could be contributing factors in this process. We hypothesized that variations in the expression of the gene network of Syntaxin 1A (STX1a) interact with early life stress (ELS), influencing the prevalence of adult depressive symptoms. Our aims were to (1) find evidence for an association between ELS and depressive behavior in adult female rats, using prepubertal social isolation (postnatal days 21-28) as a model of early adversity, and (2) create a biologically-informed polygenic risk score (ePRS) based on the network of genes co-expressed with STX1a in the prefrontal cortex, evaluating their effect on depressive symptoms (CESD collected at different moments after delivery: 6-72 months) in a cohort of women (185 participants, MAVAN cohort) exposed or not to trauma during childhood (Child Trauma Questionnaire, CTQ). In rats, isolation stress during the prepubertal period induced increased immobility in the Porsolt test in adult female rats. In humans, a GEE analysis showed an interaction between the ePRS-STX1A and CTQ ($P<0.0001$), in which women with low ePRS score are resilient to depressive symptoms, even with high trauma exposure. Early life stress interacts with genetics in determining susceptibility/resilience to depression, suggesting that the gene network co-expressed with the synaptic protein Stx1a in sensitive periods influences the resilience to this disease in adulthood even in the presence of ELS.

2-C-92 *Downregulation of molecules involved in inhibitory neurotransmission in a NHE6 knock-out model of Christianson Syndrome*

Andy Gao[1], Louis-Charles Masson[1], Talia James[1], Anne McKinney[1]

[1]McGill University

Christianson Syndrome (CS) is an X-linked neurodevelopmental disorder characterized by intellectual disability, epilepsy, and ataxia. CS arises from mutations in the Slc9a6 gene encoding sodium/proton exchanger isoform 6 (NHE6), an endosomal pH regulator that is important for protein trafficking. Yet, how the loss of NHE6 function leads to the hyperexcitability of neuronal circuitry in CS remains unknown. To this end, we investigated markers of disrupted excitatory/inhibitory (E/I) balance in adult NHE6 KO mice. In their hippocampi, we found a significant downregulation of glutamate decarboxylase 67 (GAD67), a crucial enzyme in γ-aminobutyric acid (GABA) synthesis, as well as significant losses of parvalbumin- and

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somatostatin-positive inhibitory interneurons, compared to wild-type (WT) mice. We then probed for molecules involved in inhibitory postsynaptic neurotransmission and saw losses of the ionotropic GABAA receptor α2 subunit, the inhibitory scaffolding protein gephyrin, and K/Cl cotransporter 2 (KCC2). In line with this, we also observed altered miniature inhibitory postsynaptic current amplitude and kinetics between WT and KO cornu ammonis 1 (CA1) neurons. Interestingly, whole-cell patch clamp recordings revealed a significant increase in action potential firing following current injections of increasing magnitude in KO CA1 neurons, suggesting that these cells are also intrinsically hyperexcitable. Overall, we report pre- and post-synaptic mechanisms through which E/I imbalance may develop in CS, potentially leading to seizure onset in patients.

2-C-93 *Investigating how ALS-linked mutations in MATR3 cause neurodegeneration*

Ching Kao[1], Rebekah van Bruggen[2], Claudia Arndt[1], Jeehye Park[3]

[1]Peter Gilgan Centre for Research and Learning, [2]University of Toronto, [3]The Hospital for Sick Children

Amyotrophic lateral sclerosis (ALS) is a disease characterized by motor neuron degeneration leading to progressive muscle weakness and paralysis, and typically death within 3 to 5 years of onset. Over thirty genes are associated with ALS and about half encode RNA-binding proteins (RBPs), suggesting that dysregulation of RNA metabolism plays a key role in ALS pathogenesis. Matrin-3 (MATR3) is an ALS-linked RBP involved in the regulation of alternative splicing. It is not clear how ALS-linked MATR3 mutations contribute to neurodegeneration and ALS pathogenesis. Therefore, we investigated how mutant MATR3 causes neurodegeneration by expressing human wild-type or mutant MATR3 in flies and mice. Flies that overexpress mutant MATR3 in motor neurons have decreased lifespan and climbing ability compared to flies that overexpress wild-type MATR3. To further characterize these flies, we are investigating whether mutant MATR3 promotes motor neuron degeneration and MATR3 aggregation and insolubility. Mice that overexpress wild-type or mutant MATR3 exhibit motor coordination defects and reduced muscle strength. Importantly, they also show MATR3 aggregates in the cortical neurons and microglia activation in the cortex. We will continue to follow disease progression and pathological changes in the motor neurons and muscles. Both flies and mice that overexpress mutant MATR3 show motor deficits reminiscent of ALS and will be useful to study the mechanisms underlying MATR3-associated ALS.

2-C-94 *Differential expression meta-analyses of genes identified in genome-wide association studies of depression*

Wennie Wu[1], Etienne Sibille[1], Leon French[1]

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[1]Centre for Addiction and Mental Health

In Canada, almost one in twenty people over 15 years old reported symptoms that met the criteria for major depressive disorder (MDD) in the preceding year. Globally, the World Health Organization found that depression is the largest contributor to years lived with disability. Recently, Howard et al. reported results of the largest genetic study of depression, which involved over 240,000 cases. Of the 269 genes identified, only a few have been previously investigated in the context of MDD. To better characterize these genes, we tested for differential expression in MDD cases versus controls. We used three independent postmortem studies of depression that assayed genome-wide expression in several brain regions. Additional analyses were performed for only cortical regions and each sex. Fisher's method was used to combine the direction of effect and p-values across and within the three studies. Preliminary results highlight down-regulation of Sprouty RTK Signaling Antagonist 2 (SPRY2) and up-regulation of Inositol 1,4,5-Trisphosphate Receptor Type 3 (ITPR3) in MDD cases. We did not observe a clear correspondence between differential expression and degree of genetic association within these top genes. To gain specificity, we will examine these genes in single cell studies of MDD. In summary, integration of past transcriptomic studies has prioritized several genes for follow-up studies of depression.

2-C-95 *Acting at a distance: Medulloblastoma secreted ligands disrupt normal neural stem cell function*

Alexander Gont[1], Jaclin Simonetta[1], Jenna Park[1], Alice Shan[1], Freda Miller[1], David Kaplan[1]

[1]The Hospital for Sick Children

Long-term cognitive impairments are common in pediatric brain cancer survivors. While these impairments are thought to arise following radiation treatment, recent reports suggest a link to tumour-specific mechanisms. We therefore hypothesised that pediatric brain tumours, more specifically medulloblastoma (MB), can directly affect neural stem and precursor cell (NSC/NPC) function in the forebrain by secreting bioactive factors. Mice harboring subcutaneous flank MB tumours had fewer proliferating NSCs in the V-SVZ than controls as well as decreased olfactory bulb neurogenesis and white matter oligodendrogenesis. To assess the effects of the MB secretome in the brain, concentrated conditioned media from MB cell lines (MB-CM) was injected intracerebroventricular (ICV) into mouse pups. ICV injection of MB-CM decreased NPC proliferation as well as decreased numbers of V-SVZ neurospheres in culture. MB-CM from multiple cell lines decreased V-SVZ neurosphere number and promoted astrocyte differentiation in culture. To identify the ligands contributing to the phenotype, an interaction model was developed extracting ligands from MB microarray data, networking them to receptors on NSCs. Of the predicted ligands, IL6-family cytokine expression and secretion was validated in MB cells, and when added in culture, recombinant IL6, IL11, and CT1 decreased neurosphere number.

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Overall, this work demonstrates that medulloblastoma secretes bioactive compounds that perturb neural stem cell function and the circuity involved in normal cognitive function.

2-C-96 *Molecular adaptations of the blood-brain barrier promoting depression and stress resilience*

Katarzyna Anna Dudek[1], Laurence Dion-Albert[1], Manon lebel[1], Katherine Le Clair[2], Ellen Tuck[1], Carmen Ferrer Perez[3], Sam A. Golden[4], Naguib Mechawar[5], Scott J Russo[2], Caroline Menard[1]

[1]CERVO Brain Research Centre, [2]Icahn School of Medicine at Mount Sinai, [3]University of Valencia, [4]University of Washington, [5]McGill University

Major depressive disorder (MDD) is the leading cause of disability worldwide and will affect 20% of individuals. MDD is a recurrent condition and only 30% of patients remit completely. This low efficacy level suggests that conventional treatments do not address causal biological factors. Clinical studies report higher prevalence of MDD in patients suffering from vascular diseases, indicating that increased inflammation and vascular dysfunction may contribute to depression pathogenesis. We showed that chronic stress induces blood-brain barrier (BBB) leakage in the nucleus accumbens (NAc) of mice, promoting depression-like behaviors. Here, we characterized molecular adaptations underlying stress susceptibility (SS) vs resilience (RES) in the NAc endothelial cells of C57Bl6 mice. Mice were subjected to 10-day chronic social defeat stress followed by social interaction test to determine behavioral phenotype. NAc punches were collected and cell-specific magnetic activated cell sorting was performed followed by transcriptome-wide gene-level expression analyses. We observed specific gene expression patterns in endothelial cells of the NAc of SS vs RES. Such changes were also present in RES vs control mice indicating that BBB molecular adaptations are necessary to maintain its integrity under chronic stress. We confirmed changes in BBB-related gene expression in postmortem NAc of MDD patients supporting a role for the vasculature in depression and possibly novel therapeutic strategies. Funding: NARSAD, Canada First Research Excellence Fund, FRQS, CERVO, Fonds Hélène-Hallé U.Laval

2-C-97 *Assessment of cerebrovascular proteins involved in amyloid-β disposition in a mouse model of sporadic Alzheimer's disease*

Kaitlyn Tresidder[1], Brian Bennett[1]

[1]Queen's University

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We have developed an oxidative stress-based model of late onset Alzheimer's disease (AD) based on gene deletion of aldehyde dehydrogenase 2 (Aldh2). These knockout (KO) mice exhibit age-related cognitive impairment and AD-like biochemical pathologies in both the brain and in the cerebral vasculature, including amyloid β (Aβ) deposition in cerebral microvessels. Our objective was to assess whether vascular oxidative stress alters cerebrovascular proteins involved in Aβ disposition. Using a mechanical dispersion and filtration technique, we obtained cerebral microvessels (CMVs) from 3, 6, 9, and 12-month old Aldh2 KO mice and age-matched, wild type (WT) littermates. Immunoblot analysis of these CMV preparations indicated an absence of the neuronal and oligodendrocyte markers NeuN and Olig2, the presence of the astrocyte marker, GFAP, and a strong signal for smooth muscle α-actin. We are currently assessing the basal levels of a number of proteins involved in the formation (nicastrin), catabolism (neprilysin), or transport (LDL receptor-related protein 1, LRP1) of Aβ. Preliminary immunoblot analysis of CMV preparations indicates no significant differences between WT and KO (n=4 per group) for nicastrin or LRP1 at any of the ages assessed. We are following this up with activity assays to determine whether there are differences in the function/activity of these proteins. These studies will increase our understanding of the degree to which vascular oxidative stress contributes to the AD-like pathological changes observed in Aldh2 KO mice.

2-C-98 *Exercise and 4-AP work as an effective combination therapy in a mouse model of spinocerebellar ataxia type 6*

Anna Cook[1], Sriram Jayabal[2], Kristen Vieira-Lomasney[1], Alanna Watt[1]

[1]McGill University, [2]Stanford University

Spinocerebellar ataxia type 6 (SCA6) is a late-onset polyglutamine expansion disorder characterised by ataxia and later neurodegeneration. The pathophysiology is little understood and is caused by an expanded CAG tract in the CACNA1A calcium channel gene. Treatment options are limited but our lab has recently identified several potential therapies. Using a knock-in mouse model with a pathogenic variant of the CACNA1A gene containing an expanded CAG repeat (84Q), we have shown that these mice display significant deficits in motor behaviour at 7 months, accompanied by a reduction in Purkinje cell firing precision and frequency. We first identified the drug 4-Aminopyrimidine (4-AP) as a potential treatment, since chronic oral administration caused a partial rescue of Purkinje cell firing precision and motor behaviour (Jayabal et al., 2016). We next showed that a program of voluntary exercise also elicited a partial rescue of motor behaviour. In contrast to 4-AP, however, exercise improved Purkinje cell firing frequency without affecting firing precision. These two therapies were therefore ideal candidates for a combination therapy approach in the SCA6 mouse model. By combining 4-AP drug treatment with exercise we were able to rescue deficits in Purkinje cell firing frequency and precision as well as motor behaviour. Our results suggest that both Purkinje cell rate and precision deficits contribute to SCA6

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pathology, and that a combination therapy approach may be optimal to improve motor coordination and cerebellar deficits in SCA6.

2-C-99 *Numb prevents neurodegeneration by regulating intraneuronal Tau levels in an isoform-specific manner*

Marine Lacomme[1], Katarina Stevanovic[1], Therence Bois[1], Jenny Cai[1], Michel Cayouette[1]

[1]Institut de Recherche Clinique de Montreal (IRCM)

Intraneuronal accumulation of Tau oligomers is largely recognized as an important toxic factor linked to neuronal cell death. Various post-translational modifications of Tau were found to promote oligomer formation, but how exactly intraneuronal Tau levels are regulated in health and disease remains unclear. Here we show that the endocytic adaptor protein Numb is essential to control Tau levels in mouse retinal ganglion cells (RGCs). Conditional inactivation of Numb (cKO) in RGCs caused a sharp increase in monomeric and oligomeric Tau levels in optic nerves, significant axonal blebbing, and eventual neuronal cell loss in old mice. Interestingly, siRNA-mediated knock-down of Tau in Numb cKO RGCs rescued neuronal cell death, suggesting that the increased Tau levels renders Numb cKO RGCs more susceptible to degeneration. Importantly, we found that all four isoforms of Numb can interact with Tau, but only one was able to decrease intracellular Tau levels in a reporter cell line. To test whether this Numb isoform could be neuroprotective, we overexpressed it in the RGCs of mouse models of tauopathy in vitro and in vivo. Remarkably, we found that Numb was able to reduce the number of axonal blebs in mutant RGCs in culture. In vivo, three days after NMDA injury, Numb-treated mutant mice had 50% more RGCs than control-treated mutant mice, and similar numbers of RGCs than wildtype mice. Taken together, these results uncover Numb as a novel regulator of Tau protein homeostasis in neurons and as a potential neuroprotective agent for tauopathies.

2-C-100 *Driving the nuclear accumulation of endogenous alpha-synuclein to model Parkinson's disease in mice*

Haley Geertsma[1], Steve Callaghan[1], Maxime Rousseaux[1]

[1]University of Ottawa

Parkinson's disease (PD) and related synucleinopathies are devastating neurodegenerative disorders characterized by the accumulation of misfolded alpha-synuclein (α-syn) throughout the brain. While α-syn is natively found in the synapse and the nucleus (hence its name), data from our lab and others have shown that nuclear accumulation of α-syn is toxic and occurs in PD. The toxic mechanism(s) of nuclear α-syn remain(s) elusive. To this end, we have created a mouse in

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which endogenous flag-tagged α-syn is localized to the nucleus via a nuclear localization signal (NLS) tag. Characterizing this novel α-syn-NLS-flag mouse will provide insight into the potentially neurotoxic effects of endogenous nuclear-localized α-syn. We are characterizing this mouse line on behavioural, histological, and biochemical levels to determine whether these mice phenocopy aspects of synucleinopathy over time (up to 18 months of age). Motor and non-motor tests will determine whether α-syn-NLS-flag mice exhibit dysfunction as they age. We will describe the histological findings from a young cohort of mice in efforts to determine whether α-syn nuclear accumulation causes neurodegeneration in the nigrostriatal tract (a principle site of cell loss in PD). We will present biochemical analyses to determine whether nuclear α-syn is pathologically phosphorylated and/or misfolded. Determining the presence and extent of the neurotoxic effects of nuclear-localized α-syn provides a meaningful step forward in elucidating the mechanisms of neurotoxicity that are involved in PD and related synucleinopathies.

2-C-101 *Identifying candidate ALS-risk genes through high content screening for TDP-43 mislocalization.*

Terry Suk[1], Emily MacInnis[1], Jean-Louis Parmasad[1], Steve Callaghan[1], Stephen Baird[2], Maxime Rousseaux[1]

[1]University of Ottawa, [2]Childrens Hospital of Eastern Ontario Research Institute

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease of the motor neurons. Although the majority of ALS cases are sporadic with no known cause or genetic inheritance, almost all cases display cytoplasmic mislocalization and aggregation of the RNA binding protein, TDP-43. What drives cytoplasmic accumulation of TDP-43 in ALS, however, remains unclear. Identifying the forces underlying cytoplasmic mislocalization of TDP-43 will not only provide insight into the modes of toxicity but could also shed light onto novel ALS genes and potential avenues of interception. We generated cell lines that label endogenous TDP-43 (TARDBP locus) with GFP using a CRISPR/Cas9 knock in approach. We ensured that the TDP 43-GFP fusion does not impact native TDP-43 function by looking at its localization, levels, and downstream targets. Building on this new cell line, we are making additional clones containing ALS-linked mutations (Q331K, M337V, and G348C) by editing TARDBP in cis with the GFP tag. As a proof of principle, we are using an siRNA library against the human kinome coupled with high content imaging to identify modifiers of TDP-43 localization. Further studies will validate these findings in cells with patient mutations, animal models, and will cross-reference to genetically relevant ALS cases to identify putative ALS-driving genes.

2-C-102 *Promoting endogenous photoreceptor regeneration in the mammalian retina*

Camille Boudreau-Pinsonneault[1], Michel Fries[2], Awais Javed[2], Michel Cayouette[3]

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[1]McGill University, [2]IRCM, [3]Institut de Recherche Clinique de Montreal (IRCM)

Regenerating the retina using endogenous stem cells is a promising therapy for vision restoration. While fish Müller glial cells (MG) can regenerate the retina, this natural ability was lost in mammals. Recently, however, some genetic manipulations in mouse MG were found to trigger neuron production, but it remains unknown whether MG can generate cone photoreceptors, which are essential for high acuity vision. Interestingly, MG have a similar gene expression profile to late-stage retinal progenitors, and our previous work identified temporal identity factors that can reprogram late progenitors to produce early-born cones. We hence hypothesized that these factors might reprogram MG into cone-producing progenitors. We co-electroporated Cre-dependent constructs into GlastCreERT;RosaYFPfl/fl retinal explants, which express CreERT specifically in MG, allowing expression of genes of interest and cell lineage tracing with the YFP reporter. Of the 21 combinations tested, one was able to reprogram MG into immature cones. MG-derived cells migrated to where cones normally reside, downregulated glial markers, started expressing the cone marker RxRγ, and adopted a cone-like morphology. These factors were also sufficient to reprogram MG to immature cones in vivo in the adult mouse retina, and into more mature cones under certain culture conditions. It remains to be determined whether these cells are functional, but this work suggests that stimulating cone production from endogenous glia might represent a new therapeutic opportunity for retinal degeneration.

2-C-103 *The 15q13.3 gene OTUD7A regulates multiple neurodevelopmental disorder signaling networks*

Brianna Unda[1], Savannah Kilpatrick[1], Sansi Xing[1], Vickie Kwan[1], Nicholas Holzapfel[1], Leon Chalil[1], Nadeem Murtaza[1], Elizabeth McCready[1], Yu Lu[1], Brad Doble[1], Stephen Scherer[2], Karun Singh[1]

[1]McMaster University, [2]The Hospital for Sick Children

The 15q13.3 microdeletion region is a copy number variation (CNV) associated with multiple neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD), epilepsy, schizophrenia, and intellectual disability. Using whole-genome sequencing, human brain gene expression and a mouse model with a syntenic heterozygous deletion (Df(h15q13)/+), we identified one of the 10 genes, OTUD7A, as a critical gene regulating neurodevelopmental phenotypes in the 15q13.3 microdeletion. Specifically, we found that OTUD7A regulates cortical neuron dendrite and dendritic spine formation. To study how OTUD7A may contribute to the heterogeneity of the 15q13.3 microdeletion syndrome, we used a proximity-based proteomics system, BioID2, to compare the protein-interaction networks of wildtype OTUD7A and two NDD-associated OTUD7A mutations; one found in an ASD patient and one found in an infantile epilepsy patient. Strong OTUD7A interactors included a number of scaffold proteins and receptors localized to the axon initial segment and the post synaptic density, most of which are associated

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with various NDDs. Both OTUD7A mutations showed shared and distinct changes in binding to target proteins compared to wildtype OTUD7A. Current experiments are aimed at investigating the functional impact of OTUD7A binding to target proteins, which will help identify mechanisms by which a single driver gene can drive heterogeneous phenotypes seen in patients with a CNV.

2-C-104 *Intratumoral modulation therapy effectively enhances multi-modality treatment platforms for pediatric diffuse intrinsic pontine glioma*

Andrew Deweyert[1]

[1]University of Western Ontario

Intratumoral modulation therapy (IMT) is a putative new treatment modality that delivers non-ablative electrical stimulation directly into tumor-affected brain regions to induce tumor cell death. We have previously shown that low amplitude, intermediate frequency IMT reduces glioblastoma (GBM) burden both in vitro and in vivo [Di Sebastiano et al 2018] and now aim to access IMTs therapeutic potential for the pediatric brain tumor diffuse intrinsic pontine glioma (DIPG). We hypothesize that targeted IMT in combination with chemoradiotherapy will provide an effective means to increase drug sensitivity and reduce the viability of patient-derived DIPG cells. DIPG cells were treated with either 72 hours IMT using a continuous sinusoidal waveform (200 kHz, 4V), temozolomide (TMZ), radiation (RT) or the combination of IMT, TMZ, and RT, in our established in vitro model. Cell viability was assessed with MTT viability assay and flow cytometry. MTT assay revealed a significant loss of metabolic viability in patient-derived DIPG cells treated with IMT compared to sham conditions in vitro (>40% vs. sham; n=4, $p<0.01$). TMZ and RT revealed a modest 19% and 28% reduction in cell viability respectively but increased significantly to 80% with concomitant IMT (>80% vs. sham; n=3, $p<0.001$). This study provides first-time evidence of DIPG cell susceptibility to a non-ablative electrical therapy and demonstrates the potential of IMT to effectively enhance multi-modality treatment platforms currently available for this devastating disease.

2-C-105 *Therapeutic effects of embryonic and neonatal docosahexaenoic acid supplementation in the fragile X mouse model*

Jason Arsenault[1], Octavia Yifeng Weng[2], Chengye Yang[2], Yi-Mei Yang[3], Lu-Yang Wang[1]

[1]The Hospital for Sick Children, [2]SickKids Research Institute, [3]University of Minnesota

The Fragile X syndrome (FXS) is caused by attenuated level or loss of the Fragile X Mental Retardation Protein (FMRP; Fmr1 gene), a translational regulator and ionic channel modulator. We have discovered in Fmr1 knockout (Fmr1 KO) mice that deletion of FMRP downregulates

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Kv1.2 channels at the terminals of inhibitory interneurons, resulting in excessive GABAergic inhibition of spontaneous firings of Purkinje neurons in the cerebellum (Yang, Arsenault et al. Mol Psychiatry 2018). Docosahexaenoic acid (DHA), one of the most abundant polyunsaturated fatty acid (PUFA) in the brain, can directly upregulate Kv1.2 channel activity and reverse this inhibitory overtone. Here, we administered this DHA systemically through diet supplementation (0.5% DHA w/w) and a calorically-equivalent control chow to pregnant and nursing dams (C57/BL6J WT and Fmr1 KO), as well as to post-weaned pups to investigate the neurodevelopmental impact on neurotransmission and autistic-like behaviours, complemented by immunochemical analyses of excitatory and inhibitory synaptic markers (e.g. PSD95, Gephyrin, mGluR5, Gat1, Kv1.2 and FMRP). Preliminary results reveal effects on locomotor hyperactivity, sensorimotor gating, as well as non-social anxiety from early exposure to DHA supplementation, while excessive presynaptic GABA release from interneurons was attenuated to enhance spontaneous firings of Purkinje neurons. Our results implicate DHA not only as lipid nutrients in promoting brain neurodevelopment but also as a potential therapeutics for FXS or other autism spectrum disorders.

2-C-106 *ALS-linked MATR3 S85C mutation causes motor deficits in mice*

Jihye Rachel Kim[1], Rebekah van Bruggen[1], Jeehye Park[2]

[1]University of Toronto, [2]The Hospital for Sick Children

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by degeneration of motor neurons in the nervous system, leading to muscle weakness and paralysis. Matrin 3 (MATR3), one of the most recently discovered ALS genes, was found aggregated in the motor neurons of ALS patients. Several mutations in MATR3 have been identified in both familial and sporadic ALS cases, but how mutant MATR3 causes ALS is still not understood. Here, we characterized a MATR3 mutation by generating mice harboring an ALS-linked mutation S85C in mouse Matr3 endogenous locus through CRISPR/Cas9. S85C homozygous mice did not show any overt phenotype during development. By 20 weeks however, these mice showed decreased body weight and hindlimb clasping. We also found that these mice exhibit motor incoordination and decreased vertical activity measured by rotarod and open field tests, respectively. Interestingly, we found increased SDS-insoluble protein levels and high molecular weight species in the cortex of S85C mutant mice, suggesting a possible mechanism of how mutant MATR3 may cause toxicity. Currently, we are conducting various behavioural tests as well as protein solubility analysis and neuropathological analysis to further characterize the progression of the disease over time. By characterizing a novel ALS-causing mutation in MATR3, we hope to gain a better understanding of the molecular mechanisms underlying neurodegeneration, thus providing insights into developing novel therapeutic approaches.

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2-C-107 *Characterizing behavioural changes in a primate model of alzheimer's disease*

Robert Wither[1], Susan Boehnke[1], Robert Marino[1], Ron Levy[1], DJ Cook[1], Fernanda De Felice[1], Douglas Munoz[1]

[1]Queen's University

There is an urgent need to develop new animal models for Alzheimer's disease (AD) to vet new therapeutic strategies. To this end, we have developed a non-human primate (NHP) model of AD via intracerebroventricular (icv) injection of neurotoxic amyloid beta oligomers (AβOs). This model recapitulates key molecular aspects of human AD pathology: tau hyperphosphorylation, tangle formation, synaptic loss, and astrocytic activation. Here, we describe behavioural changes in male rhesus macaques that have either received large volume icv injections once a month for 12-18 months or a sequence of smaller icv injections 3x per week for 3 weeks. Using a cage-side touch-screen adapted version of the human CANTAB battery, we tested the cognitive profile of AβO injected NHPs using tasks that assessed focused attention, spatial working memory, visual discrimination, and paired associates learning capacities. We also monitored home-cage behavior, examining the circadian rhythms and behavioral patterning of the NHPs using a 3-D accelerometer activity tracker and 24/7 video. We identified deficits on the self-ordered spatial search task in macaques following AβO injection. Furthermore, we observed that injected NHPs had difficulty learning new tasks (delayed match to sample and paired associated learning) and had reduced home-cage activity. Overall, we have identified several behavioural abnormalities in an NHP model of AD that are reminiscent of what is observed in human AD.

2-C-108 *Altered circadian modulation of neurotransmission in bipolar mouse model*

Alesya Evstratova[1], Tiago Soares Silva[1], Martin Beaulieu[1]

[1]University of Toronto

Bipolar disorder affects more than 2% of general population and manifests itself as mood changes from depression to manic states with different duration and severity. Recent studies reveal association between disrupted circadian rhythms and increased risks of mood instability, including bipolar disorder (Ferguson et al., 2018, Lyall et al., 2018). One of the well accepted animal models of bipolar disease, is ClockΔ19 line, which has a point mutation in the Clock gene and is characterized by "manic-like" phenotype, normalized by lithium treatment (Roybal et al., 2007, Enkhuizen et al., 2013). We used ClockΔ19 mice housed at normal and reversed light/dark cycle to study pyramidal neuron activity using whole cell patch clamp recordings in the acute brain slices of PFC. Our data indicate that mutant clock mice exhibit disruption of circadian change in the neuronal activity. They do not show increase in the sEPSC amplitudes during dark phase (DP), characteristic of wild type mice (WTs). Moreover, while neurons from WTs generate larger and faster action potentials during DP compared to light phase (LP) , neurons from mutant mice during

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LP generate action potentials which are significantly larger and faster compared to WTs and they stay similar during DP. Altogether these leads to the increased firing rates of Clock mutant neurons in response to depolarization during DP, and therefore alters circadian modulation of neurotransmission. The results of this study will help to better understand cellular mechanisms of bipolar disorder and its dependence on the circadian rhythms.

2-C-109 *Increased seizure susceptibility after traumatic brain injury in zebrafish*

Sung-Joon Cho[1], Eugene Park[2], Andrew Baker[2], Aylin Reid[1]

[1]University Health Network, [2]St Michael's Hospital

Objective: Post-traumatic epilepsy (PTE) is defined as recurrent seizures occurring one week after traumatic brain injury (TBI). Animal studies of PTE are cost-intensive and time-consuming. Zebrafish (ZF) are known as a suitable model organism for studying human pathophysiology due to their ease of use, and require less maintenance than rodents. Here, we propose that the cost-effective ZF would serve as a suitable PTE model to bridge the gap between in vitro studies and low-throughput animal studies. Methods: We used pulsed high-intensity focused ultrasound to induce severe TBI in AB strain wild-type ZF (6-10 months old). Injured ZF and naïve controls were monitored by video for spontaneous seizure activity over the next 14 days, and a seizure susceptibility test was performed using a sub-convulsive dose of 2.5 mM pentylenetetrazole (PTZ) on 7 or 14 days post-injury (DPI). Results: 100% of the TBI group developed spontaneous myoclonic-like jerking behaviour and 83% developed clonic-like prolonged jerking behaviour by 14 DPI (n=23). Such behaviours were not detected in the naïve group (n=9). The latency to reach clonic-like seizures after PTZ administration was significantly shorter in the TBI versus naïve ZF. After PTZ 90% of injured ZF had clonic-like seizures at 7 DPI (n=10) and 100% at 14 DPI (n=10), versus 22% of the naïve group (n=9). Conclusion: This study is the first to demonstrate increased seizure susceptibility as well as spontaneous behavioural seizure activity after TBI in ZF, suggesting this may be a useful model for studying certain aspects of PTE.

2-C-110 *Novel zebrafish models to understand respiratory depression and analgesia by opioids*

Shenhab Zaig[1], Carolina Scarpellini[1], Xiao-Yan Wen[1], Gaspard Montandon[1]

[1]St. Michael's Hospital

Objectives: Opioids are the mainstay of pain management but cause lethal respiratory depression. Developing safe opioid pain therapies producing analgesia without side-effects is therefore critical. To accelerate drug discovery, we developed zebrafish models of respiratory depression

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and analgesia by opioids. Methods: To assess analgesia, we recorded swimming behaviour in zebrafish larvae (12-14 days post-fertilization) in response to the nociceptive stimulus formalin (0.05%), the μ-opioid receptor agonist fentanyl (0.2μM) and the antagonist naloxone (5μM). To determine respiratory depression, we recorded buccal movements and measured respiratory activity in response to opioids and stimulants. Results: Fentanyl decreased the increase in swimming caused by formalin (P=0.02,n=8), compared to formalin alone, and naloxone blocked the fentanyl's effect (P=0.024,n=7). Fentanyl significantly decreased breathing rate (baseline: 36±5 breaths/min, fentanyl: 8±4 breaths/min, P=0.001,n=9), an effect blocked by naloxone (63±4 breaths/min, P=0.001). Preliminary data showed that respiratory stimulants, ampakine CX614 and 5-HT4 agonist BIMU8, increased respiratory rate when administered with fentanyl. Discussion: Our results suggest that fentanyl reduces pain and depresses breathing in zebrafish, as observed in mammals. Our zebrafish models can be used for a high-throughput phenotype-based screening platform to identify pain therapies without respiratory depression.

2-C-111 *Fly genetic screen reveals modifiers of MATR3 toxicity*

Melody Zhao[1], Hongxian Zhu[1], Rebekah van Bruggen[1], Jeehye Park[2]

[1]University of Toronto, [2]The Hospital for Sick Children

MATR3 is an RNA binding protein and nuclear matrix protein in which over a dozen mutations are implicated in neuromuscular diseases such as distal myopathy, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. MATR3 S85C is the first and most common mutation identified in autosomal-dominant distal myopathy, later reclassified as ALS. In addition, MATR3 pathology has been found in both neurons and muscles. However, the pathways and mechanisms of how mutations in MATR3 cause disease remain unknown. To investigate this, our lab developed a fly model that expresses MATR3 in the indirect flight muscles. Flies expressing wildtype MATR3 display mild wing position defects and muscle degeneration, and flies expressing mutant MATR3 display increased penetrance and expressivity of these phenotypes. Interestingly, both wildtype and mutant MATR3 are localized in the nucleus, but mutant MATR3 is less soluble than wildtype MATR3. Flies expressing MATR3 S85C display ~50% abnormal wing position, thus we used this mutant to perform a targeted candidate screen which identified over 50 genetic enhancers that increase the penetrance of the abnormal wing phenotype. Several enhancers increase MATR3 protein levels and further decrease mutant MATR3 solubility. To investigate the mechanisms involved, we plan to analyze the effect of modifiers on MATR3 mRNA expression, protein stability and localization. Together, this work may shed light on the biological pathways and mechanisms underlying MATR3-associated neuromuscular diseases and provide clues for potential therapeutic targets.

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2-C-112 *Pyrimidinergic signaling alterations in the Fragile X Syndrome mouse cortex*

Kathryn Reynolds[1], Chloe Wong[1], Laurie Doering[1], Angela Scott[1]

[1]McMaster University

The neurological symptoms of Fragile X Syndrome (FXS) partly arise due to aberrant glial-neural communication driven by dysregulation of astrocyte-secreted synaptic proteins. One such astrocyte-secreted protein, thrombospondin-1 (TSP-1), promotes the development of immature excitatory synapses in the cortex. TSP-1 expression and secretion are regulated through UTP-induced activation of pyrimidinergic P2Y receptors; however, the impact of pyrimidinergic signaling in FXS remains unclear. Using the fmr1 knockout (fmr1-/-) mouse model of FXS, we observed elevated TSP-1 expression in both fmr1-/- postnatal cortex and fmr1-/- cortical astrocyte primary culture. Following treatment with 0.1 uM-100 uM UTP, Western blotting and immunocytochemistry revealed elevated intracellular TSP-1 expression in both wildtype (fmr1 /) and fmr1-/- astrocytes. While wildtype astrocytes displayed a linear dose-response relationship between TSP-1 expression and UTP concentration, knockout astrocytes exhibited maximal TSP-1 expression even at the lowest UTP dose. The fmr1-/- astrocytes also secreted greater quantities of TSP-1 than their wildtype counterparts following UTP-mediated activation. Quantitative protein analysis of pyrimidinergic receptor expression showed elevated levels of P2Y2 and P2Y6 receptors in fmr1-/- astrocyte primary culture, as well as in isolated astrocyte fractions from fmr1-/- mouse cortical tissue, compared to wildtype expression. These results suggest that pyrimidinergic signaling is differentially regulated in fmr1-/- astrocytes and may have therapeutic relevance to FXS.

2-C-113 *Synaptic dysfunction in human neurons with autism-associated deletions in PTCHD1-AS*

P Joel Ross[1], Wenbo Zhang[2], Kirill Zaslavsky[3], Eric Deneault[3], Rebecca Mok[2], Lia D'Abate[2], Deivid Rodrigues[2], Ryan Yuen[2], Wei Wei[2], Alina Piekna[2], Peter Pasceri[2], Rebecca Landa[4], Michael Salter[2], Stephen Scherer[2], James Ellis[2]

[1]University of Prince Edward Island, [2]The Hospital for Sick Children, [3]University of Toronto, [4]Kennedy Krieger Institute

The Xp22.11 locus that encompasses PTCHD1, DDX53, and the long noncoding RNA (lncRNA) PTCHD1-AS is frequently disrupted in males with autism spectrum disorder (ASD), but the functional consequences of these genetic risk factors for ASD are unknown. To evaluate the functional consequences of PTCHD1 locus deletions, we generated induced pluripotent stem cells (iPSCs) from unaffected controls and two ASD subjects with microdeletions affecting PTCHD1-AS/PTCHD1 or PTCHD1-AS/DDX53. Function of iPSC-derived cortical neurons was assessed using electrophysiology, which revealed that iPSC-derived neurons from the ASD subjects

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exhibited reduced frequency of AMPA receptor-dependent miniature excitatory post-synaptic currents (AMPAR-mEPSC). We compiled novel and known genetic variants of the PTCHD1 locus to explore the roles of PTCHD1 and PTCHD1-AS in genetic risk for ASD and other neurodevelopmental disorders, and we found 35 ASD-associated deletions that disrupt exons of PTCHD1-AS. We also report a novel ASD-associated deletion of PTCHD1-AS exon 3, and we show exon 3 loss alters PTCHD1-AS splicing without affecting expression of the neighboring PTCHD1 coding gene. Finally, targeted disruption of PTCHD1-AS exon 3 recapitulated diminished AMPAR-mEPSC frequency, supporting a role for the lncRNA in the etiology of ASD. Our findings provide further evidence that PTCHD1-AS deletions are genetic risk factors for ASD, and implicate PTCHD1-AS both in the function of excitatory synapses and in ASD-associated synaptic impairment.

2-C-114 *Examining the physiological mechanisms of rTMS-induced EEG alpha suppression in depressed patients with connectome-based neural mass modelling*

John Griffiths[1], Peter Fettes[2], Jonathan Downar[2], Jeremie Lefebvre[3]

[1]Centre for Addiction and Mental Health, [2]University Health Network, [3]Krembil Research Institute, University Health Network

Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment for patients with major depressive disorder (MDD), with clear advantages over pharmacological and psychotherapeutic alternatives in terms of time, specificity, and side-effects. However, the mechanisms underlying the efficacy of rTMS in MDD remain very poorly understood. In this study we analyzed EEG data from MDD 30 patients undergoing 30 days' experimental rTMS therapy using a novel stimulation site (right orbitofrontal cortex). Sensor-space analyses of resting-state EEG power spectra indicated a significant pre- vs. post-rTMS decrease ($p<0.05$ corrected) in alpha (8-12Hz) power at multiple sensor locations, with a left posterior focus. The magnitude of this decrease was correlated with improvement in symptoms. To investigate the mechanisms of this rTMS-induced EEG alpha suppression, we employed a recently-developed thalamocortical neural mass model of EEG rhythms, which is able to capture a variety of typical M/EEG data features. The observed suppression of alpha activity was explained in the model by an increase in sensory/neuromodulatory drive to the thalamus, coupled with modulations of the strength of connectivity between the thalamus and the cortex. We discuss our results in the context of network-level and 'non-reward attractor' characterizations of MDD, and also in the light of broader psychological and systems neuroscience perspectives on alpha rhythms as a 'default' brain state, that is antagonistic to cognition-related high-frequency cortical activity.

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2-C-115 *The role of Natural Killer cells in mediating the effects of Maternal Immune Activation on offspring brain and behaviour*

Faraj Haddad[1], Cleusa De Oliveira[1], Susanne Schmid[1]

[1]University of Western Ontario

Maternal infection and the associated immune response during pregnancy are known risk factors for neurodevelopmental disorders such as autism spectrum disorder (ASD) and schizophrenia in the offspring. In rodents, maternal immune activation (MIA) by pathogen-free immune stimulation in pregnant mothers produces brain and behavioral deficits in the offspring. However, the contribution of the placenta in MIA mechanisms is poorly understood. Natural Killer (NK) cells are immune cells present in the uterus and placenta and may play a role in MIA pathophysiology. We induced MIA using the viral mimic polyinosinic: polycytidylic (poly I:C) at gestation day 9.5 in either wild type (WT) rats or NK knockout rats. We hypothesized that poly I:C MIA will differentially affect offspring brain morphology and behavior in adolescence (6 weeks) and adulthood (3 months) depending on whether they are bred by WT or homozygous knockout parents. We tested the offspring in social behaviour, open field exploration and habituation and multimodal prepulse inhibition of the acoustic startle reflex. We also sought to determine microglial number and activation at each age-point using immunostaining. Preliminary results show age and sex-specific deficits in startle reactivity, long term startle habituation and social behavior. Some of these effects seem to be absent in NK knockout rats, but further testing is in progress to account for litter effects and confirm the maternal immune response. Our results will help elucidate the role of NK cells in mediating MIA's effects on neurodevelopment.

2-C-116 *Dysfunction of NMDA receptors in neurons derived from human induced pluripotent stem cells with deletions of PTCHD1-antisense long noncoding RNA*

Wen-Bo Zhang[1], P. Joel Ross[2], Eric Deneault[3], Kirill Zaslavsky[1], Wei Wei[1], Alina Piekna[1], Peter Pasceri[1], Stephen Scherer[1], James Ellis[1], Michael Salter[1]

[1]The Hospital for Sick Children, [2]University of Prince Edward Island, [3]University of Toronto

Autism Spectrum Disorder (ASD) is a common, early onset neurodevelopmental disorder with impairment in social communication, language and cognition. The causes of ASD are complex with multiple contributing factors including genetic variants, which play key roles in the occurrence of ASD. Previous studies discovered that PTCHD1-antisense (PTCHD1-AS) long noncoding RNA (lncRNA) gene, located in the X-linked PTCHD1 locus, is frequently disrupted in patients with ASD, indicating that PTCHD1-AS lncRNA might be an ASD candidate gene. The cellular consequences of this disruption on neuronal function remain unknown. To investigate dysfunction of PTCHD1-AS lncRNA, we utilized the neurons derived from human induced-pluripotent stem cells from an unaffected control and two people with ASD - one with deletions of both PTCHD1 and PTCHD1-

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AS lncRNA and one with a deletion of only PTCHD1-AS lncRNA. Patch-clamp recordings from these neurons revealed no significant differences in input resistance, the resting membrane potential, and action potential parameters between neurons derived from the control and those from the ASD subjects. However, NMDAR currents, recorded at both negative membrane potential in the absence of extracellular magnesium and positive membrane potential in the presence of magnesium, were decreased in neurons from both of the ASD subjects compared those from the unaffected control. Our findings are the first functional data characterizing the role of ASD candidate gene, PTCHD1-AS lncRNA in human neurons and provide a basis for identifying potential therapeutic targets.

2-C-117 *Transcriptional profiling of a presymptomatic Rett syndrome mouse model*

Laura Hergott[1], Stephanie Kyle[1], Neeti Vashi[1], Monica Justice[1]

[1]The Hospital for Sick Children

Rett syndrome (RTT) is a rare neurological disorder, mostly caused by sporadic mutations in the X-linked gene methyl-CpG-binding-protein-2 (MECP2), a master transcriptional modulator. Girls with RTT develop normally for about 6-18 months, followed by developmental stagnation and regression. Several mouse models recapitulate RTT and although heterozygous (Mecp2/+) female mice may be more clinically relevant, hemizygous males (Mecp2/Y) are the preferred model as they exhibit a completely penetrant phenotype. Transcriptional changes have been examined in symptomatic Mecp2/Y brains, but the results lack reproducibility. In spite of years of study, the molecular events that initiate RTT are unknown and treatment options remain limited. To distinguish the transcriptional changes that occur exclusively due to the loss of Mecp2 as a transcriptional regulator rather than being altered as a result of the diseased state, RNA-sequencing was performed on five specific brain regions of presymptomatic (postnatal day (P) 23) and symptomatic (P45) 129S6SvEv/Tac Mecp2tm1.1Bird/Y mice with their age-matched wildtype littermates. Already, numerous misregulated molecular pathways have been identified in distinct brain regions solely presymptomatically. Following validation, this outcome will guide single cell RNA-sequencing to identify the specific cell-type and initial mechanism for RTT onset. The findings will provide insight into both the early pathophysiology of RTT and normal MECP2 function, and may also reveal novel therapeutic targets for early RTT treatment.

2-C-118 *Accelerated forgetting of previously acquired fear memory after repeated PTZ seizures*

Lianne Brandt[1], Hugo Lehmann[1], Neil Fournier[1]

[1]Trent University

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Mesial temporal lobe epilepsy is the most prevalent form of drug refractory epilepsy, and over half of patients report some aspect of memory and learning problem. One type of memory deficit that is particularly common is accelerated long-term forgetting (ALF), which is characterized by an initially normal acquisition and retention of memories over short periods of up to 30 minutes, but abnormally fast forgetting over periods of days or weeks after the event. Despite the prevalence of memory retention deficits among epileptic patients, the neurobiological mechanisms contributing to these problems remain obscure. In the present study, we examined the impact of repeated seizures on the long-term retention of previously acquired contextual fear memory. In this study, 23 male Sprague Dawley rats underwent contextual fear learning task and showed robust fear memory recall when re-tested. Three days after training, one group of rats underwent chemical kindling for 2 weeks with the chemoconvulsant pentylenetetrazole (PTZ) and a retention test was conducted 4 days after the last seizure. When compared to non-kindled controls, we found that PTZ-treated rats exhibited significantly less freezing behaviour upon re-testing suggesting that seizures induced forgetting of the fear memory. We are currently examining the role that aberrant synaptic remodelling within hippocampal circuits plays in mediating the impairments in retrieving previously acquired fear memory.

2-C-119 *Direct lineage reprogramming of astrocytes to oligodendrocytes*

Justine Bajohr[1], Kevin Lee[1], Alexandra Traister[1], Maryam Faiz[1]

[1]University of Toronto

Direct lineage reprogramming in the central nervous system (CNS) is the forced conversion of one neural cell type to another. It offers the unparalleled ability to replenish cells lost to CNS disease or injury. Many studies have focused on converting astrocytes given their contribution to the pathology of neurological conditions. To date, astrocyte-based reprogramming strategies have typically been used to generate new neurons. However, there is also a clinical need to replace oligodendrocytes (OLs) that are lost or damaged after injury. It is therefore of interest to determine the factors required for astrocyte reprogramming to functional OLs. Using lentiviral delivery of transcription factors important for OL development, we show that astrocytes can be converted to OLs in vitro within 14 days and express markers of the OL lineage. These findings lay the groundwork for a novel strategy to treat diseases and injuries that result in the loss of OLs, such as stroke, spinal cord injury, multiple sclerosis and Alzheimer's Disease.

2-C-120 *Subjective memory ability correlates with functional connectivity between the hippocampus and posterior default mode network in cognitively normal older adults*

Linda Mah[1], Darren Liang[1], Frankie Chan[1], Aliya Ali[1], Mirjam Mulder-Heijstra[1], Susan Vandermorris[1], Nicolaas Paul LG Verhoeff[1], Nathan Herrmann[1], J. Jean Chen[1]

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[1]University of Toronto

Purpose: Subjective memory complaints are linked with development of Alzheimer's disease (AD) but the neural mechanisms underlying this association are unclear. Multimodal neuroimaging studies suggest that large-scale network disruptions occur before amyloid plaques appear in the brain, beginning with alterations in the posterior default mode network (pDMN), including decoupling of the hippocampus (HC) from pDMN nodes (Jones et al, 2016, Brain). Here we investigated the association between subjective report of memory ability and functional connectivity of the HC and pDMN. We hypothesized that self-report of greater memory ability would be positively correlated with HC-pDMN connectivity. Methods: Participants were 45 older adults [15 males, mean age=72(6.3)] with normal cognition based on neuropsychological assessment and no neurological or psychiatric conditions. Subjective memory was evaluated using the Memory Functioning Questionnaire (MFQ). Resting state functional magnetic resonance imaging was acquired using gradient-echo EPI BOLD at 3T and processed using CONN toolbox. Seed-based analysis used an 8 mm region of the posterior cingulate cortex (PCC, x=-6, y=-52, z=40), a key node within the pDMN, to measure functional connectivity with left and right HC. Results: Total MFQ and MFQ frequency of forgetting (MFQ-FF) subscale scores were significantly correlated with left HC-PCC functional connectivity (MFQ total: r=0.36, p=0.016; MFQ-FF: r=0.48, p=0.001). MFQ-FF, but not total MFQ, scores were significantly correlated with right HC-PCC functional connectivity (MFQ total: r=0.25, ns; MFQ-FF: r=0.37, p=0.013). Conclusions: These findings suggest that subjective memory complaints reflect HC-pDMN decoupling, consistent with large-scale network disruptions early in AD.

2-C-121 *Emergence of palmitoylation as a regulator of autophagy in neurodegeneration*

Dale Martin[1]

[1]University of Waterloo

Autophagy is an essential pathway that removes toxic proteins and damaged organelles from the cell, but is disrupted in many neurodegenerative diseases, leading to build up of toxic and aggregated proteins. Although many regulators of autophagy are known, how they rapidly transition from the cytoplasm to their target membranes upon autophagy activation is not well understood. A potential unifying mechanism in autophagy and neurodegeneration is palmitoylation, the reversible post-translational addition of fatty acids, typically palmitate, to proteins, akin to phosphorylation. The hydrophobic lipid promotes membrane binding, protein-protein interactions, and protein stability. Hypothesis: Palmitoylation provides a rapid and dynamic mechanism for membrane recruitment of autophagy regulators during autophagy. Preliminary bioinformatic analysis shows that autophagy is significantly enriched in palmitoylated proteins. We have now confirmed palmitoylation of several key regulators of autophagy in a variety of tissues

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and cells including human and rodent brains. Furthermore, these regulators have altered palmitoylation levels in disease models suggesting palmitoylation may provide therapeutic targets in these diseases. Impact: This work provides a link between the role of palmitoylation in directing autophagy proteins to membranes and clearance of toxic proteins by autophagy in neurodegeneration. This will increase our understanding of autophagy regulation and how autophagy contributes to homeostasis in the nervous system as well as providing insight into targeting palmitoylation in the nervous system.

2-C-122 *Relationship between dorsolateral prefrontal brain activation and microstructure in patients with schizophrenia*

Christin Schifani[1], Colin Hawco[1], Arash Nazeri[2], Daniel Blumberger[1], Zafiris Daskalakis[1], Aristotle Voineskos[1]

[1]Centre for Addiction and Mental Health, [2]Washington University School of Medicine

Cognitive impairment, particularly working memory (WM), is a core feature of schizophrenia and predict functional outcome. Various studies link WM deficits to alterations in dorsolateral prefrontal cortex (DLPFC) brain activation and recent evidence suggests a relationship between WM and DLPFC microstructure in schizophrenia. Despite this converging evidence, no study has investigated the relationship between brain microstructure and function in schizophrenia. In the present study, we used baseline MRI data from 45 patients with schizophrenia (n=48 had diffusion-weighted and functional scans, n=3 did not pass QC), enrolled in an rTMS treatment trial. All scans were acquired prior to treatment. BOLD (Blood-Oxygen-Level-Dependent) imaging of an N-back WM task was used to estimate task-based brain activation. General linear models were run using SPM contrasting 3-back (high WM) to 1-back (low WM). Grey matter microstructure was examined using multi-shell diffusion-weighted imaging and the neuritic orientation dispersion and density imaging (NODDI) model, which provides indices of neuritic orientation dispersion (ODI) and density (NDI). Values for NDI, ODI and BOLD contrast for bilateral DLPFC were extracted and associations were explored using Pearson's linear correlations. Preliminary analysis revealed significant associations between BOLD activation and microstructure. In the right DLPFC, patients with stronger BOLD contrast had higher NDI ($r=0.30$, $p=0.043$) and lower ODI ($r=-0.31$, $p=0.037$). These findings provide the first direct evidence for an association between brain microstructure and BOLD activation to a WM task in patients with schizophrenia. Future studies should examine brain microstructure as a possible biomarker of response to WM enhancing treatments.

D - Sensory and motor systems

2-D-123 *Sensorimotor behaviour in the connexin-35b (Cx35b) knock-out zebrafish (danio rerio)*

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Cherie Brown[1], Christiane Zoidl[1], Georg Zoidl[1]

[1]York University

In rodents, connexin-36 (Cx36) is the major component of electrical synapses, also found alongside chemical synapses in mixed synapses throughout the vertebrate brain. Our research characterizes the contribution of Cx36 to learning, memory and sensorimotor circuitries in an animal model suitable for fundamental and statistically-strong in-vivo studies. The zebrafish (Danio rerio) is ideal for this purpose as a well characterized model for genetic, developmental and behavioral studies. Here, targeted ablation of the Cx36 ortholog Cx35b was achieved using Cas9/CRISPR-technology. Homozygous Cx35b knock-out (KO) fish showed no morphological abnormalities and bred normally. Sensorimotor phenotypes were determined in six-day old (6dpf) larvae, when all major brain areas, including sensory organs, are developed which allows testing of locomotor behavior under different light conditions. Locomotor activities like burst, freeze, and total swim duration were compared to age-matched wild-type (WT) larvae. Cx35b-KO larvae were less active under various white light intensities, demonstrating a reduction in total swim duration. Specifically, the duration and count of burst activity, was significantly lower in Cx35b-KO larvae suggesting an impairment in signal propagation in the visual sensory and/or motor systems where Cx35b is expressed. In support, larvae freeze duration increase despite having a lower number of freeze events in Cx35b KOs. We concluded that Cx35b is critical in modulating neuronal circuity underlying normal sensorimotor behaviours.

2-D-124 *Temporal processing of multisensory events: predicting cybersickness in virtual reality*

Ogai Sadiq[1], Michael Barnett-Cowan[1]

[1]University of Waterloo

Humans are constantly presented with rich sensory information that the central nervous system (CNS) must process to form a coherent perception of the world. While the CNS may be efficient in doing so in natural environments, virtual reality (VR) poses challenges for the CNS to integrate multisensory information. Although VR systems are becoming widely used, VR exposure often causes cybersickness in users, possibly due to temporal discrepancies between multiple sensory events. As large individual differences in the perceived simultaneity of multisensory events have been reported in the literature, here we sought to assess if individual differences in perceived temporal order judgement (TOJ) of multisensory cues can predict cybersickness in VR. We conducted two TOJ tasks where participants judged the temporal order of audio-visual (AV) or audio-head movement cues to measure the temporal binding window (TBW) and the point of subjective simultaneity (PSS). Participants subsequently explored two VR environments and cybersickness levels were quantified using the Simulator Sickness Questionnaire (SSQ). Results

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indicate a positive correlation between the AV PSS and SSQ, suggesting that the time required for light to precede sound to be perceived as simultaneous may predict cybersickness in VR. We also find a trend that those with a wider AV TBW may be more susceptible to cybersickness. We conclude that shared sensory processing mechanisms subserve both temporal processing and cybersickness, but further analysis is needed to fully characterize these mechanisms.

2-D-125 *Dominant vs non-dominant hand differences in early somatosensory evoked potentials in response to a novel motor tracing task*

Mahboobeh Zabihhosseinian[1], Ryan Gilley[1], Danielle Andrew[2], Bernadette Murphy[3], Paul Yielder[1]

[1]University of Ontario Institute of Technology, [2]University of Waterloo, [3]University of Ontario Institute of Technology (UOIT)

The dominant (Dom) and non-dominant (Non-Dom) limbs behave differently during training in a novel dynamic environment with the Non-Dom favoring feedback control and the Dom preferring feedforward mechanisms. Differences in hemispheric cortical excitation projected onto the two limbs reflect differences in neural pathways. Early somatosensory evoked potentials (SEPs) offer a validated, non-invasive mechanism to explore possible differences in sensorimotor integration (SMI.) We sought to explore possible differences in early sensorimotor processing between the right (Dom) and left (Non-Dom) hand in healthy right handed participants. SEPs were recorded in response to median nerve stimulation at baseline and post motor acquisition. Two groups (Dom vs. Non-Dom) of 12 participants completed a novel motor acquisition tracing task. One group trained with their Dom hand and the other group with their Non-Dom hand. The Non-Dom was significantly more accurate at baseline ($p<0.0001$). There was a significant effect of time ($p<0.0001$) for the tracing task, with significant group interactions for the N24 ($p<0.001$) and the N30 ($p<0.0001$) SEP peaks. Post motor acquisition the Dom hand had a 28.9% decrease in the N24 and a 23.8% increase in the N30 with opposite directional changes for the Non-Dom hand; 22.04% increase in N24 and 24% decrease in the N30. These indicate the differences in early SMI between Dom and Non-Dom hands in response to motor learning outcomes related to the underlying neural mechanisms and preferences adopted by the limbs when performing upper limb movements.

2-D-126 *Anatomical and physiological characterization of the claustrum-retrosplenial cortex circuit*

Brian Marriott[1], Jesse Jackson[1]

[1]University of Alberta

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The claustrum (CLA) is a small, highly connected subcortical brain region that has been linked to many higher order cognitive processes such as attention and sleep. While the general connectivity of the claustrum has been explored previously, precise characterization of each projection pathway remains lacking. One such connection is the link between the retrosplenial cortex (RSC) and the claustrum. The RSC is involved in various types of memory and rapid eye movement sleep, and previous research has shown significant claustrocortical projections to this area. Our goal is to further characterize the anatomical and physiological basis of this connection in mice. To address anatomy, we used retrograde adeno-associated viruses (AAVs), cholera toxin B subunit (CTB), and Fast Blue to retrogradely label claustrum projection neurons sending inputs to different rostro-caudal regions of the RSC. In addition, retrograde injections were made to analyze layer specificity of CLA-RSC projections. To determine the physiological basis of CLA-RSC projecting cells, we used single and 32-channel electrophysiology to record the activity of the RSC while optogenetically stimulating either ipsi, contra, or bilateral CLA-RSC projecting neurons. We will compare and contrast the claustrum projection to the RSC and PFC to examine the magnitude and fidelity of feedforward inhibition and inhibitory neuron excitation.

2-D-127 *Substrates for caudal-rostral gradient of operational switch in larval zebrafish swimming circuits*

Stephanie Gaudreau[1], Yann Roussel[2], Vanessa Gallo[1], Melissa Paradis[1], Benjamin Lindsey[3], Tuan Bui[1]

[1]University of Ottawa, [2]École Polytechnique Fédérale de Lausanne, [3]University of Manitoba

As animals develop, motor control becomes more refined and complex. The mechanisms within the spinal cord that underlie locomotor development are not yet well understood. Since the emergence of the zebrafish (Danio rerio) as an attractive vertebrate model for developmental studies, it has been demonstrated that chemical neurotransmission is first utilized by spinal locomotor circuits in later embryonic stages, and the role of specific neurotransmitters rapidly evolves over developmental time. For instance, glycine becomes increasingly more important for the generation of tail beat rhythm as the zebrafish matures and that, surprisingly, the timing of the emergence of glycine for rhythmogenesis has a caudal to rostral gradient over the length of the spinal cord. We sought out to determine other caudo-rostral gradients in the same developmental window. First, we asked whether there was a caudo-rostral gradient in secondary motoneuron population density, using the Zn8 antibody for immunohistochemical staining. Secondary motoneurons are later born motoneurons involved in slower locomotor movements that emerge at the same time that glycine becomes important for rhythmogenesis. Next, we wondered if this same caudal-to-rostral progression of glycine dependent rhythmogenesis was associated with changes in glycinergic synapses. To determine whether there is an increase in glycinergic synapses onto motoneurons at caudal segments first, immunohistochemical staining was

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performed using a GlyT2 antibody. Our findings further detail the various mechanisms that govern motor maturation.

2-D-128 *Dissecting long-range reinforcement signals to GABAergic interneurons in the motor cortex*

Candice Lee[1], Simon Chen[1]

[1]University of Ottawa

Motor learning is a complex process that relies on neural circuit plasticity to encode new memories but the spatiotemporal rules that govern and drive this plasticity are not well understood. GABAergic interneurons exert fine control over cortical gain through both inhibition and disinhibition of selected neurons. In the primary motor cortex (M1), two major classes of GABAergic interneurons, SOM and PV interneurons, undergo opposing plastic changes during motor learning, demonstrating subtype-specific plasticity among GABAergic interneurons. VIP interneurons are a third major GABAergic subtype and primarily inhibit SOM interneurons, thereby disinhibiting pyramidal neurons. To understand whether and how each GABAergic interneuron subtypes integrate learning related information in M1, we have performed in vivo two-photon calcium imaging in awake and behaving mice while the animals receive unpredicted rewards. Our preliminary data shows that unanticipated reward uniformly activates VIP-INs, whereas random movements do not. In addition, we have conducted cell-type specific retrograde tracing using the engineered rabies system to unveil brain-wide inputs to different M1 interneuron subtypes. We propose that long-range reinforcement signals may be propagated through different inhibitory interneuron subtypes and together, gate local circuit plasticity that is important for the formation of new memories.

2-D-129 *Distinct expression patterns of Acid - Sensing Ion Channels in mouse primary sensory afferents*

Melina Papalampropoulou-Tsiridou[1], Feng Wang[1], Yves de Koninck[1]

[1]Université Laval

Acid- Sensing Ion Channels (ASICs) are implicated in normal functions and pathological conditions of the central and peripheral nervous system. Four genes (ASIC1-4) encoding 6 different subunits (ASIC1a, ASIC1b, ASIC2a, ASIC2b, ASIC3 and ASIC4) through alternative splicing have been identified in rodents. ASIC1, ASIC2 and ASIC3 are expressed in dorsal root ganglia (DRGs) in adult mice, however, their detailed expression pattern has not been investigated yet. In this study, we combined a highly sensitive in situ hybridization technique with

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immunohistochemistry to identify expression of ASICs in different populations of sensory neurons within the DRG. More specifically, we targeted peptidergic nociceptors (Calcitonin gene-related peptide, CGRP+), non-peptidergic nociceptors, (Isolectin IB4, IB4+), and myelinated sensory afferents within the DRG (Neurofilament 200, NF200+). Based on our results, ASIC1a and ASIC1b appear to display similar expression patterns. They were expressed in about 28% of CGRP+ and 72% of NF200+ neurons, but not in IB4+ neurons. In contrast, ASIC2a and ASIC2b showed different expression patterns. ASIC2a was expressed in about 70% of IB4+, 11% of CGRP+ and half of NF200+ neurons. ASIC2b was expressed in almost all DRG neurons, including all IB4+ and CGRP+ neurons, as well as 80% of NF200+ neurons. Finally, ASIC3 is mostly expressed in NF200+ neurons and of the majority of CGRP+ neurons. In conclusion, different ASICs show distinct expression patterns in DRG neurons, indicating that they may be involved in coding different types of sensory modalities.

2-D-130 *Back to the basics: Mapping the activated neurons in a mouse model of parkinson's disease*

Alysia Ross[1], Shawn Hayley[1], Hongyu Sun[1]

[1]Carleton University

P Parkinson's disease (PD) is a neurodegenerative disorder resulting from progressive degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SNc). This is thought to result in a decrease of SNc DA innervation to the striatum and consequently affect the direct and indirect basal ganglia pathways. Pesticides, particularly the herbicide paraquat, have been shown to contribute to the pathogenesis of PD. Work in rodents has demonstrated that systemic administration of paraquat results in degeneration of SNc DA neurons coupled with the hallmark motor symptoms of PD. However, how this loss affects basal ganglia circuitry is not clearly understood. Here, we hypothesize that the paraquat-induced degeneration of SNc DA neurons results in the activation of specific groups of striatal neurons. To test this hypothesis, we used a paraquat mouse model of PD in c-fos based transgenic mice to map the activity of neurons in the nigrostriatal pathway. We found that paraquat exposure results in increased neuronal activity only in a selective group of neurons in the striatum. This is evidenced by specific activity-dependent GFP tagging, which is coupled with a significant decrease in motor activity. Our results demonstrate a selective group of overactive neurons in the striatum and suggest that these active neurons may play a key role in mediating the dysregulated inhibition of other brain regions resulting in the motor symptoms of PD.

2-D-131 *Prevalence of BDNF polymorphism in musicians: evidence for compensatory motor learning strategies in music?*

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Tara Henechowicz[1], Leonardo Cohen[1], Joyce Chen[1], Michael Thaut[1]

[1]University of Toronto

The study compared the prevalence of Val66Met BDNF SNP polymorphism (r6265) in musicians in professional training (N=41) to an ethnically matched general population sample from the 1000 Human Genome Project (N=424). The polymorphism has a typical prevalence of 25-30% and is associated with deficits in motor learning and neuroplasticity (Joundi et al., 2012; Kleim et al., 2006). One may predict that musicians have reduced prevalence compared to the general population due to the high motor skill demands of music. DNA was extracted from saliva samples and genotyped for the SNP rs6265 (BDNF; Val66Met). Genotypic and allelic frequencies were not between groups. Genotypic Frequency: G/G 62.74% Controls vs 58.54% Musicians; A/G 33.25% Controls vs 39.02% Musicians; A/A 4.01% Controls vs 2.44% Musicians (p=0.76). Allelic Frequency: G Allele 79.36% Controls vs 78.05% Musicians; A Allele 20.64 % Controls vs 21.95% Musicians (p=0.90). There were no significant age differences in musicians. However, Met-Carriers had $\bar{x}$=3.3 more years of primary instrument training (p<0.05). Presence of the polymorphism did not bias against high-end motor skill learning in music. Characteristics of music motor learning may compensate for genotype predisposition. Significantly greater primary instrument training in Met-carriers may represent possible compensatory differences. Since the polymorphism is associated with decreased rates of stroke recovery (Kim et al., 2016) data may have relevance for clinical translations of music-based training to stroke rehabilitation.

2-D-132 *Chronic and acute pain sensory system of the African naked mole-rat*

Sandra Poulson[1], Melissa Holmes[1], Loren Martin[1]

[1]University of Toronto Mississauga

Chronic forms of pain manifest differently in young children compared to adults. Following nerve injury, children recover better and are less likely to develop chronic pain. Thus, to further explore the development of chronic pain during pre-pubertal stages, we examined hypersensitivity following nerve injury using subordinate African naked mole-rats; a species where most of the adults do not undergo puberty. Specifically, we measured responses to a mild mechanical, a strong mechanical, and a mild cold stimulus, with mice used as a comparison. Between mice and naked mole-rats, the mechanical sensitivities were similar. However, we observed an absence of response to mild cold in the naked mole-rat adults. Thus, we also tested acute responses by measuring pain behavior upon application of chemical activators of ion channels implicated in cold sensation. Mustard oil, an activator of TRPA1 evoked similar responses between the two species in pain behavior. In contrast, icilin - an activator of TRPM8 - induced a strong pain phenotype in mice but a minimal response in naked mole-rats. We followed with nucleic acid in-situ hybridization staining to compare expression of TRP ion channels (TRPA1, TRPM8 and

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TRPV1). Our results bring to view species differences in chronic and acute pain systems likely echoing divergent evolution due to environmental demands.

2-D-133 *Evidence for neocortical learning induced by sensory surprise*

Colleen Gillon[1], Jérôme Lecoq[2], Jed Perkins[2], Sam Seid[2], Carol Thompson[2], Ryan Valenza[2], Joel Zylberberg[3], Blake Richards[1]

[1]University of Toronto, [2]Allen Institute for Brain Science, [3]York University

Sensory processing in the neocortex relies on a hierarchy of regions which respond to increasingly complex stimulus features. Computational neuroscientists have postulated that through this hierarchy, the neocortex learns a generative model of its environment. Such a model would enable it to quickly predict incoming stimuli, and use these predictions for inference. If the neocortex does indeed learn a generative model, then stimuli that violate current expectations should elicit responses that are distinct from those elicited by expected stimuli. Furthermore, unexpected stimuli should induce new learning, provoking changes in their representations as the internal model is updated. To test this, we habituated mice over several sessions to two sets of stimuli with predictable global structures, namely cycling Gabor patches with jittered orientations and random bricks moving together. We then introduced surprising, unexpected stimuli, i.e. by suddenly rotating some Gabor patches or reversing the direction of some bricks, while recording somatic and dendritic responses in layer 2/3 and layer 5 neurons of primary visual cortex V1 using two-photon calcium imaging. We find that unexpected stimuli do indeed produce distinct responses with markedly different dynamics from expected stimuli. Furthermore, the responses to the unexpected stimuli show a greater change over time than the responses to expected stimuli, even within a single hour-long session. This data support the idea that the neocortex is learning a hierarchical, generative model, driven by sensory surprise.

2-D-134 *The role of GluN2D function and modulation in spinal cord pain signalling*

Christopher Dedek[1], Michael Hildebrand[1]

[1]Carleton University

The spinal cord dorsal horn (DH) is critical for the transmission and modulation of pain signals. Within the DH, NMDA receptors (NMDARs) are a key mediator of excitatory neurotransmission. The GluN2B/D subtypes of NMDARs dominate the NMDAR component of synaptic responses in lamina I DH neurons of adult rats. In a nerve injury model of neuropathic pain, GluN2B is potentiated through phosphorylation by Src family kinases (SFKs) at lamina I synapses, but the role of GluN2D is unknown. We test here whether GluN2D-containing NMDARs are functionally

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present and potentiated by SFKs at lamina I synapses of neonatal to juvenile (P8 to P21) rats - a critical developmental window for DH circuits. To isolate NMDAR-mediated synaptic responses, we performed voltage clamp recordings of miniature excitatory post-synaptic currents (mEPSCs) at 60 mV in rat spinal cord slices. Following treatment of spinal slices with pharmacological antagonists of GluN2A (10 μM TCN-201) and GluN2B (1 μM Ro25-6981), only a slow-decaying, GluN2D-like NMDAR component remains. This suggests that the GluN2D subtype mediates a fraction of synaptic responses at immature lamina I synapses. We are currently investigating whether the peptide SFK activator EPQ(pY)EEIPIA alters overall and GluN2D-mediated NMDAR responses at P8 to P21 lamina I synapses. Given that GluN2D is not prevalent in the brain, elucidating its role in synaptic transmission and plasticity within the spinal pain signalling network may reveal new therapeutic targets for modulating pain without altering other critical NMDAR-dependent CNS functions.

2-D-135 *Regulators of G-protein-signaling 4 regulate inhibition of the respiratory network by opioid ligands*

Jamil Danaf[1], Carolina Scarpellini[1], Richard Horner[2], Gaspard Montandon[1]

[1]St. Michael's Hospital, [2]University of Toronto

Objective: Opioids are widely used analgesics, but present with respiratory depression that can be lethal with overdose. Binding of opioids to μ-opioid receptors (MORs) in brainstem respiratory centers induces respiratory depression. The preBötzinger Complex (preBötC), a medullary site critical for generating breathing, regulates respiratory rate depression by opioids. G-protein-activated inwardly-rectifying potassium (GIRK) channels mediate MOR inhibition of respiratory circuits. Regulators of G-protein signaling (RGS) inhibit GIRK channel activation in various neural circuits, but their role in respiratory depression is unknown. Methods: To determine RGS4 expression in brainstem respiratory centers, we used in situ hybridization for RGS4 and MOR mRNAs in male Wistar rats. To determine the role of RGS4 in regulating MOR-induced respiratory depression, we microperfused the RGS4 inhibitor CCG 50014 and the MOR agonist DAMGO into the preBötC while recording respiratory muscle activity in anesthetized rats. Results: RGS4 was co-expressed with MOR in the preBötC, nucleus tractus solitarius, and medullary raphe, three neural sites regulating breathing. DAMGO alone decreased respiratory rate by 22.4±4.5%, while CCG 50014 and DAMGO decreased respiratory rate by 56.9±10.6%. Conclusion: RGS4 and MOR were co-expressed in key brainstem respiratory centers. RGS4 inhibition accentuates respiratory rate depression by MOR ligands, showing RGS4 may play a role in MOR-induced respiratory depression and may constitute a potential target to identify drugs that could reduce opioid side-eff

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2-D-136 *In search of the larval zebrafish striatal homologue*

Vernie Aguda[1], Michael Martin[1], Nicholas Guilbeault[1], Indira Riadi[1], Helen Chasiotis[1], Laura Koek[1], Jordan Guerguiev[1], Tod Thiele[2]

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

Inhibitory neurons within the striatum play a fundamental role in action selection and are also highly conserved across vertebrates. However, their exact location and function are not known for larval zebrafish. Based on previous studies of developmental gene expression in 2-day-old fish, it is thought that neuronal populations homologous to those of the striatum lie within the dorsal subdivision of the subpallium. Our anatomical studies located two neuronal populations in the subpallium of 7-day-old fish that are potentially homologous to the direct and indirect pathway neurons identified in mammals. Direct pathway neurons promote movement and express substance P, whereas indirect pathway neurons inhibit movement and express enkephalin. Whole mount fluorescent in situ hybridization revealed large bilateral neuronal clusters in the subpallium that express the substance P precursor gene tac1. A smaller cluster of neurons, just ventral and medial to tac1 positive neurons, express the enkephalin precursor gene penka. We are now conducting volumetric calcium imaging experiments to simultaneously examine activity in these anatomical domains while fish execute prey capture, escapes and optomotor swims. Lastly, we are inactivating these subpallial regions using laser ablation to determine if they are necessary for generating these behaviors. Together, these experiments should help establish if larval zebrafish possess circuitry homologous to the mammalian striatum, and if these circuits play a similarly central role in controlling behavioral outputs.

2-D-137 *Sex, APOE, and dementia family history: Relationship between dementia risk and cognitive-motor integration performance*

Alica Rogojin[1], Diana Gorbet[1], Kara Hawkins[1], Lauren Sergio[1]

[1]York University

Cognitive-motor integration (CMI) involves concurrent thought and action which requires the interaction of large networks in the brain. The objectives of our research are to 1) investigate the effect that dementia risk has on the ability to integrate rules into action, and 2) to examine the neural basis of CMI impairment in individuals with dementia risk. Given evidence that early-stage dementia involves neural network dysfunction, we propose that problems with CMI can be used to detect dementia in its early stages. To this end, we recruited asymptomatic male and female participants both with and without dementia risk factors (family history and presence of APOE e4 allele). Participants were tested on four visuomotor tasks, one standard condition (vision and movement targets spatially coupled) and three cognitively-demanding non-standard conditions (vision and movement targets increasingly spatially decoupled). Multiple linear regression

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analyses revealed that having an e4 allele was a significant predictor of poorer CMI performance in two of the non-standard conditions (plane-change and plane-change + feedback reversal), while both sex and family history were significant predictors of worse performance in the third non-standard condition (feedback reversal). These data suggest that the CMI task may be detecting performance decrements in individuals genetically at-risk for dementia prior to clinical symptom presentation. Furthermore, the underlying brain networks that control thinking and moving at the same time may be different between men and women.

2-D-138 *Impact of DREADD-induced inhibition of general, cholinergic and glutamatergic PPTg neurons on prepulse inhibition*

Niveen Fulcher[1], Erin Azzopardi[1], Cleusa De Oliveira[1], Roger Hudson[1], Steven Laviolette[1], Susanne Schmid[1]

[1]University of Western Ontario

Our brains consistently receive an abundance of stimuli from the environment. An innate process that filters out sensory stimuli, sensorimotor gating, can be quantified via prepulse inhibition (PPI) of the acoustic startle response. Deficits of PPI are seen in a host of psychiatric illnesses, such as schizophrenia and autism spectrum disorder (ASD). Literature suggests that chronic lesions of the midbrain pedunculopontine tegmental nucleus (PPTg) disrupt PPI and cholinergic PPTg projections to the startle-mediating caudal pontine reticular nucleus (PnC) giant neurons have been suggested to mediate PPI. The PPTg is also comprised of glutamatergic and GABAergic neurons; we therefor revisit the long-standing PPTg cholinergic hypothesis, using intracranially delivered general-, cholinergic- or glutamatergic-neuron specific inhibiting DREADDs bilaterally into the rat PPTg. Subjects were tested for startle, PPI, locomotor activity and morphine-induced conditioned place preference (CPP) after receiving an i.p. injection of DREADD activator, clozapine-N-oxide (CNO) or saline. In accordance to previous lesion studies, general DREADD inhibition disrupted PPI upon CNO administration. Surprisingly, DREADD inhibition of cholinergic PPTg neurons did not affect PPI, whereas DREADD inhibition of glutamatergic PPTg neurons disrupted PPI similarly to that of the general DREADD inhibition. Our results highlight the important role of the PPTg in sensorimotor gating and its deficits but suggest that glutamatergic and not cholinergic PPTg neurons mediate PPI.

2-D-139 *Glucose effects on intracortical and corticospinal excitability: a double-blinded, placebo-controlled study*

Stephen Toepp[1], Chiara Nicolini[1], Aimee Nelson[1]

[1]McMaster University

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Transcranial magnetic stimulation (TMS) techniques for measuring corticospinal and intracortical excitability are widely used to describe neurological diseases and injuries. However, the influence of glucose on these measures has not been thoroughly investigated despite the possibility that it could necessitate rigorous dietary controls to ensure adequate precision and reliability. The present double-blinded, placebo-controlled study tested the effects of glucose on short-interval intracortical inhibition, and motor evoked potential (MEP) recruitment curves. Dependent measures were the ratio of the conditioned to the unconditioned MEP responses, and the slope and area of MEP recruitment curves respectively. These measures were acquired by delivering TMS over the left motor cortex and recording MEPs via surface EMG over the muscle belly of the first dorsal interosseous muscle. Healthy males (n=20) each participated in four sessions. Session 1 involved familiarization to TMS, followed by acquisition of an individualized blood glucose response curve. During sessions 2, 3 and 4, dependent measures were taken before and after drinking an experimental solution containing glucose (75 g), sucralose-sweetened placebo (control for sweetness) or plain water (control for time). Post-drink measurements started 5 minutes prior to the blood glucose peak observed during Session 1. This advances the precision and reliability of TMS measurements by detailing the impact of glucose on these commonly used neurophysiological measures.

2-D-140 *Serotonin modulates feedback-mediated neural and behavioral sensory adaptation*

Mariana Marquez[1], Maurice Chacron[1]

[1]McGill University

A general principle in systems neuroscience is that sensory systems must adapt to highly dynamic natural stimuli in order to output appropriate behaviors. This adaptation is partially achieved through neuromodulators such as serotonin. Although much effort has been made towards reveling a common role of serotonin in sensory systems, this question remains unsolved. This is in part due to the complexity of establishing a link between the serotonergic effects at the cellular and organism levels and further determining whether these effects are species specific or not. In order to shed light on the functional role of serotonin in sensory processing, we took advantage of the electrosensory system of the weakly electric fish Apteronotus albifrons. Using a combination of in vivo electrophysiology, pharmacology and behavioral paradigms, we found that serotonin mediates optimized coding of natural stimuli by modulating neuronal and behavioral tuning properties to second-order natural stimuli. Due to the ubiquitous nature of both serotonergic fibers and feedback pathways in the brain, it is likely that our results are found across sensory systems.

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2-D-141 *The utilization of translational behaviours to study sensory processing in the Cntnap2-/- rat model of ASD*

Kaela Scott[1], Susanne Schmid[1], Brian Allman[1]

[1]University of Western Ontario

The processing of sensory information is necessary for interactions with our environment; however, in individuals with autism spectrum disorders (ASD), impairments in lower-level sensory filtering may impact higher-order perceptions of complex sensory signals. Thus, this study aimed to establish a preclinical animal model with high face validity for ASD-related behavioural deficits to ultimately study the mechanisms underlying sensory behaviours in ASD. Both sound intensity and multisensory processing at the pre-attentive and perceptual level were assessed in rats with a functional knockout of the Cntnap2 gene. Pre-attentive processing was examined using the acoustic startle response and its modulation by a prior stimulus (i.e., prepulse). For cognitive testing, operant conditioning was used to assess the rats' ability to discriminate the relative sound intensity of noisebursts, or timing of auditory and visual stimuli. Cntnap2-/- rats exhibited a general impairment in prepulse inhibition, with no audiovisual prepulse integration deficit. Similar to autistic individuals, the Cntnap2-/- rats showed no deficits in perceiving the relative timing of the auditory and visual stimuli compared to wildtypes. Moreover, despite Cntnap2-/- rats showing increased reflexive responses to moderately loud sounds, they had no difficulty in accurately discriminating sounds that varied in intensity. Taken together, these results confirm that the sensory processing impairments in ASD can be effectively studied in rat models using the aforementioned translational behavioural paradigms.

2-D-142 *Visual looming and receding stimuli activate a large brain network in the common marmoset*

Justine Clery[1], David Schaeffer[1], Yuki Hori[1], Kyle Gilbert[1], Joseph Gati[1], Stefan Everling[1]

[1]University of Western Ontario

The common marmoset (Callithrix jacchus) is a small-bodied New World primate that has been recently identified as a powerful model to study brain functions in addition to canonical Old World macaque monkeys. Its lissencephalic cortex allows access to many cortical regions for electrophysiological or neuroimaging technics, thus making marmosets a potentially powerful nonhuman primate model for the study of complex visual processing. Here we used functional magnetic resonance imaging (fMRI) to explore responses to looming visual stimuli in marmosets which are known to activate large networks in macaques and humans. We performed fMRI on awake marmosets in a 9.4T scanner by using visual stimuli either looming toward the animals or

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receding away from them. Both types of visual stimuli evoked large brain activations across the brain with strong activations in visual, temporal, parietal and frontal areas. However, looming stimuli elicited not only a more widespread network but also activated temporal areas, some somatosensory areas, motor areas as well as subcortical areas (amygdala). Interestingly, the majority of these activations is also found in the macaque brain when visual looming stimuli predicted a tactile stimulus (Cléry et al. 2017) highlighting an alert network. This suggest that even in absence of potential tactile stimulation, the marmoset brain is ready to treat any potential threat or impact and that this network is shared between primate species.

2-D-143 *Single unit activities in the marmoset parietal cortex during a saccadic task*

Liya Ma[1], Janahan Selvanayagam[1], Lauren Schaeffer[1], Kevin Johnston[1], Stefan Everling[1]

[1]University of Western Ontario

Abnormal saccadic eye movements are characteristic for patients with several psychiatric and neurological disorders but are difficult to study in non-primate animals. The common marmoset (Callithrix jacchus) is a promising nonhuman primate model with a lissencephalic brain, allowing for accurate targeting of brain regions that are hidden in sulci in the macaque brain. We trained two marmosets on a task in which Gap trials (stimulus onset lagged fixation spot offset by 200ms) were interleaved with Step trials (the two events were simultaneous). Both marmosets showed a gap effect commonly observed in humans, which is a reduction in saccadic reaction times (SRTs) in Gap trials compared to Step trials. Both spiking activities and local field potentials were recorded during the task through 32-channel microelectrode arrays (Utah array) implanted in the posterior parietal cortex (PPC). Among 361 isolated units we found 56 gap-modulated cells (15.5%), the activities of which changed significantly from the pre-gap fixation period to the gap period. When the stimulus was presented contralaterally to the area recorded, activities of these cells were predictive of the subsequent SRTs, and whether the response would be an express (SRT<=104ms) or regular (SRT>104ms) saccade. We also found 143 cells (40%) that displayed a significant visual response 70-120ms after stimulus onset, the intensity of which predicted the SRTs in all trial types. Our findings suggest that the common marmoset has a PPC that plays similar functional roles as the lateral intraparietal area in macaque monkeys.

2-D-144 *The mechanisms of ultra-high precision in an oscillatory neural circuit*

Aaron Shifman[1], Yiren Sun[1], John Lewis[1]

[1]University of Ottawa

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The precise timing of neuronal activity is critical to normal brain function, be it for sound localization, escape responses, or plasticity and learning. The medullary pacemaker network (PN) of the weakly electric fish sets the timing for an oscillating electric organ discharge (EOD) used for electric sensing. This network is the most precise biological oscillator known, with sub-microsecond timing variation. The PN consists of two principle sets of neurons: pacemaker and relay cells, connected by gap junctions. The degree of connectivity between these cells is insufficient to provide the population averaging required for the measured precision. Several alternative hypotheses have been proposed, including individual cells having high precision, and electric field feedback from the EOD. We are using computational tools to explore the complex dynamics underlying these hypotheses. As a first step, we are developing a model of PN neurons that generates action potential waveforms similar to those seen in intracellular recordings. We compare the model dynamics to those seen during experimental manipulations. These comparisons will provide an experimental validation of the model so that it can facilitate exploration of temporal precision in neuronal oscillators. We also present preliminary results on the role of electric field effects in PN precision.

2-D-145 *Temporally diverse glutamate signals drive direction-selective starburst amacrine cell dendrites in the mouse retina*

Zachary Turple[1], Varsha Jain[1], Tracy Michaels[1], Santhosh Sethuramanujam[1], Gautam Awatramani[1]

[1]University of Victoria

INTRODUCTION Direction-selectivity (DS) is first observed in the visual system in the radial dendrites of retinal starburst amacrine cells (starbursts). The synaptic mechanisms underlying starburst DS remain elusive. Recent connectomic analysis suggests distinct anatomical bipolar cell types are segregated along the proximal-distal axis of starburst dendrites. This has led to a space-time wiring specificity hypothesis for supporting DS (Kim et al., 2014; Nature, 509:7500). Here we aim to investigate these bipolar cells' functional properties for the first time by imaging glutamatergic input to starbursts. METHODS We developed an all optical system to stimulate and monitor glutamate release, using the glutamate-sensing fluorescent reporter iGluSnFR (pAAV.hSyn.Flex.iGluFnFr.WPRE.SV40). Starbursts were selectively targeted for iGluSnFR gene expression by intravitreal injection of a Cre-dependent rAAV plasmid into ChAT-Cre+ mice. Dim blue light stimuli activated bipolar cells via photoreceptors. Fluorescence changes were measured using two-photon microscopy on wholemount retinae. RESULTS We found simple static spot stimuli evoked sustained and transient responses in spatially segregated areas in the dense plexus formed by starburst dendrites. These responses exhibited a center-surround receptive field organization that was reduced by TTX and abolished by GABAA/C receptor blockade, as well as distinct contrast sensitivities. Surprisingly, although these responses were not DS, they did exhibit

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motion sensitivity for which the basis will be investigated pharmacologically. CONCLUSIONS Our data indicate that temporally diverse bipolar cells exhibiting sustained and transient glutamate signals drive starburst dendrites, supporting the space-time wiring hypothesis for retinal DS.

E - Homeostatic and neuroendocrine systems

2-E-146 *Sequenom sequencing identifies SNPs associated with anhedonia and fearfulness in rats*

Li Li[1], Zi Han Wang[2], Oscar Vasquez[3], Maria Aristizabal[3], Nick O'Toole[1], Irina Pokhvisneva[1], Josie Diorio[2], Amsale Belay[4], Marla Sokolowski[3], Tie Yuan Zhang[1], Michael Meaney[1]

[1]McGill University, [2]Douglas Institute, McGill University, [3]University of Toronto, [4]Clinical Genomics Cneter

Genome-wide association studies identify risk genetic loci associated with pathophysiology of psychiatric disorders in human. However, current animal models of psychiatric disorders introduce extreme manipulations such targeted null mutations or overexpression, which do not reflect the more subtle effects of SNPs on gene expression. We probed candidate regions of the outbred Long-Evans rat genome for single nucleotide polymorphisms (SNPs) associated with anhedonia and fearfulness using Sequenom sequencing. We found that rs198664367 (Ampk) and rs13448419 (Creb3l1) were significantly associated with fearfulness and anhedonia behaviors, respectively. Animals with CA genotype in Ampk gene show increased total center time in novelty suppressed feeding (NSF) test compared to CC genotype. Animals with GC genotype in Creb3l1 gene show increased latency to food in NSF compared to GG genotype. Furthermore, different genotypes of rs198862086 (Nr3c1) differentially mediate the effect of postnatal maternal behavior on fearfulness of offspring. For AA genotype, there is a positive association between maternal care and total center time in NSF in adult males, but not in females. For AT and TT genotypes, there is a negative association between maternal care and total center time in NSF in adult females, but not in males. These findings provide evidence of SNP association as well as interaction between genetic variations and early life environment for phenotypic outcomes in rats and provide a model for the study of the biological mechanisms underlying genotype - phenotype associations.

2-E-147 *Perinatal high-fat diet alters the neuroendocrine stress response to neonatal immune activation*

Mouly Rahman[1], Ceren Sogukpinar[1], Patrick McGowan[1]

[1]University of Toronto

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From neonatal life through adulthood, the offspring of mothers consuming high levels of saturated fats (HFD) during pregnancy and lactation show evidence of immune activation, increased stress-related behaviours, and altered hypothalamic-pituitary-adrenal (HPA) neuroendocrine stress responses. These persistent effects suggest that perinatal HFD alters developmental programming of the HPA axis, a system that also affects immune response. Since HFD offspring display enhanced basal immune activity, and since susceptibility to stress-induced programming is highest in perinatal life, we hypothesize that neonates exposed to HFD will have a potentiated stress response to neonatal immune activation (NIA), and this stress response will re-program the HPA axis. The aim of our study was to characterize immediate and persistent outcomes of NIA using lipopolysaccharide to simulate bacterial infection in rat neonates exposed to HFD. Levels of the stress hormone corticosterone (CORT), stress-related gene expression in the hypothalamus and hippocampus, and stress-related behaviour were examined. Neonates exposed to HFD exhibited increased stress-related behaviour and altered stress-related gene expression in the brain in response to NIA compared to controls. Juveniles exposed to both HFD and NIA also showed increased stress-related behaviour and lower basal levels of CORT. These findings suggest that maternal obesity predisposes neonatal offspring to a potentiated response to immune activation, which may shape HPA axis function and related behaviours later in life.

2-E-148 *Examining the interplay between inflammation and endocannabinoids in the amygdala during colitis*

Haley Vecchiarelli[1], Kaitlyn Tan[2], Vincent Chiang[2], Maria Morena[2], Min Qiao[2], Catherine Keenan[2], Samantha Baglot[2], Robert Aukema[2], Gavin Petrie[2], Quentin Pittman[2], Keith Sharkey[2], Matthew Hill[2]

[1]University of Calgary, Hotchkiss Brain Institute, [2]University of Calgary

It is well-established that there is a link between chronic inflammatory diseases and stress-associated psychiatric disorders, however, the mechanisms underlying this link are not fully elucidated. In order to investigate this interplay, we utilize a rodent model of inflammatory bowel disease, in adult, male, Sprague Dawley rats. We have previously shown that there is a reduction in anandamide (AEA) levels, driven by CRF-R1 induced increase in its metabolic enzyme, fatty acid amide hydrolase (FAAH), seven days following colitis onset. Furthermore, we have shown that the anxiety-like behavior co-morbid with colitis at seven days can be reversed by acutely augmenting AEA levels. To further explore if these changes in endocannabinoid signaling could also relate to alterations in neuroinflammatory processes, we next examined changes in the protein levels of key inflammatory mediators (IL-1β, IL-6, MCP-1), and found these molecules to all be elevated within the amygdala at three days following colitis onset, with no changes at seven days. Temporally, this increase in inflammatory molecules occurs prior to the reduction of AEA levels in the amygdala, which we had previously demonstrated occurs at seven days following

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colitis onset, but not three days. Given the link between CRF and inflammation, we are currently investigating the relevance of this increase in inflammatory mediator production to the increase in FAAH activity and reduction of AEA levels necessary for colitis-induced anxiety.

2-E-149 *Dietary fructose induces synaptic plasticity at Neuropeptide Y neurons*

Mikayla Payant[1], Jenny Campbell[1], Alex Hebert[1], Eleftheria Maratos-Flier[2], Melissa Chee[1]

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

Increased sugar consumption has been linked to rising obesity rates. Table sugar, or sucrose, is a disaccharide comprised of one fructose and one glucose molecule; but it is not known if fructose and glucose have equivalent roles in the etiology of obesity, as both molecules can act in the hypothalamus to regulate central energy balance. Within the hypothalamus, activating neurons that express Neuropeptide Y (NPY) in the arcuate nucleus drive feeding and stimulate weight gain. We thus determined if fructose and glucose act at NPY neurons to promote diet-induced obesity. We fed mice a high fructose diet (HFrD, 60%), high dextrose diet (HDxD, 60%) or standard chow and found that only HFrD-, but not HDxD-fed mice, ate more calories, had lower baseline locomotor activity, and gained more body fat than chow-fed mice. We then performed patch-clamp recordings to determine if HFrD or HDxD feeding alters the excitability of NPY neurons. While neither HFrD nor HDxD feeding altered the firing rate of NPY neurons, HFrD-feeding increased excitatory synaptic input to NPY neurons. This synaptic plasticity emerged within one week and persisted over four weeks of continued HFrD feeding. However, HDxD feeding did not induce such synaptic plasticity. When HFrD-fed mice were returned to a chow diet, the HFrD-mediated synaptic input also reversed upon the cessation of HFrD feeding. These findings indicate that HFrD, but not HDxD feeding, leads to the development of diet-induced obesity and suggest that dietary fructose promotes an obesogenic phenotype through synaptic plasticity at NPY neurons.

2-E-150 *Estimation of chromatin state and transcription factor dynamics across sex, estrus cycle, and puberty in the mouse hypothalamus*

Dustin Sokolowski[1], Huayun Hou[1], Liis Uuskula-Reimand[1], Dustin Sokolowski[1], Cadia Chan[1], Anna Roy[1], Anna Goldenberg[1], Mark Palmert[2], Michael Wilson[2]

[1]University of Toronto, [2]The Hospital for Sick Children

Puberty is a crucial developmental period marked by sexual maturation and the production of gametes through activation of the hypothalamic-pituitary-gonadal axis. The timing of pubertal

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onset varies across sex and ethnicity; these variations have been associated with sex-specific health complications in later life. Yet, despite its importance, the mechanisms underlying pubertal onset are not well understood. Pubertal onset coincides with large changes in gene expression controlled by alterations in transcription factor (TF) activity. To investigate mechanisms of pubertal onset, we measured hypothalamus gene expression (RNA-seq) and epigenetic markers (ChIP-seq: H3K4me2, H3K27me3, H3K27ac, and H3K36me3) before/after puberty in mice of both sexes and at both stages of estrus cycle in post-pubertal females only. We integrated epigenetic data from the four histone posttranslational modifications to create a chromatin state map of the mouse hypothalamus. We then identified regions with a change in chromatin state and nucleosome repositioning across puberty and sex before completing TF motif enrichment. We found that 11 transcription factors are significantly enriched for genes with repositioned nucleosomes and alterations in chromatins states when comparing across sex, including Egr1, and Esra which also have a plausible role in puberty. We are currently testing Egr1 and Esra to investigate their combined role in sex-differentiation and puberty using ChIP-seq.

2-E-151 *CRH-PVN neurons decode stress controllability and control voluntary escape*

Nuria Daviu Abant[1], Tamas Fuzesi[1], David Rosenegger[2], Neilen Rasiah[2], Toni-Lee Sterley[1], Govind Peringod[2], Jaideep Bains[2]

[1]University of Calgary, [2]Hotchkiss Brain Institute

Innate behaviors do not require learning but are sensitive to prior situational experience. Here we show that innate defensive behaviors can be reprioritized even if the original and subsequent experiences are unrelated. This context independent learning relies on shifts in the activity of CRHPVN neurons. Specifically, we show that CRHPVN anticipates the initiation of voluntary, unlearned escape behavior in response to different threats; silencing CRHPVN during threat decreases escape behavior. Further, the response to threat can be manipulated bi-directionally by experiences in which there are differential representations of control. Exposure to situations in which there is no outcome control diminishes CRHPVN anticipatory activity, decreasing subsequent escape behavior. By contrast, situations with high outcome control increase CRHPVN anticipatory activity, increasing escape behavior in an unrelated context. These observations indicate that CRHPVN is necessary for voluntary escape behavior and use information from prior, unrelated experiences to modify innate defensive behaviors to threat.

2-E-152 *Neural mechanisms linking hypernatremia to circadian time*

Claire Gizowski[1], Charles Bourque[1]

[1]McGill University

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While clock time is normally adjusted by daylight onset, it can also be regulated by non-photic stimuli through unknown mechanisms. In this project, we examined if hypernatremia can acutely regulate clock time. The organum vasculosum lamina terminalis (OVLT) is a preoptic nucleus that contains neurons capable of detecting hypernatremia. We therefore examined if OVLT neurons can modulate SCN clock neurons. Histological and tracing experiments showed that sodium-sensitive OVLT neurons project to the SCN. Interestingly, SCN VP neurons primarily receive GABAergic synaptic events. Further tracing experiments indicated that sodium-sensitive GABA OVLT neurons project to the SCN. Preliminary results suggest GABA excites SCN VP neurons during wake time, when SCN electrical activity is low. Electrophysiological analysis in slices further revealed that a hypernatremic stimulus delivered to the OVLT significantly increases the frequency of spontaneous GABA synaptic currents and triggers an anticipatory shift in the onset of electrical activity in SCN clock neurons. These data show that the SCN not only drives circadian rhythms, but also receives important physiological signals that can mediate non-photic adjustments in clock time and possibly adapt organisms to dynamic environments.

2-E-153 *Multiscale neurobiological pathways to comfort food consumption in response to stress*

Andre Portella[1], Zhenfeng Ma[2], Laurette Dube[1]

[1]McGill University, [2]Wilfrid Laurier University

Stress induced preference for comfort food is one factor behind the overconsumption of fat and sugar and the current obesity epidemics. Traditional research has traditionally explored this under a psychological perspective alone, whereas stress reactions are known to be an embodied experience consisted of psychological, hormonal, and neurophysiological components. We hypothesized that whole body response to stress would better predict palatable food preference than psychological state alone following acute stress. 40 healthy women aged 58 /-7.8y were tested in a within-subjects design. Participants were exposed to control condition (neutral imagery) on session 1 and stress (health stress mental imagery) on session 2, separate one week apart. After the task subjects were presented with snack buffet and had consumption recorded. Measurements were mood (Profile of Mood States (POMS-SF)), heart rate variability (HRV), skin conductance and salivary cortisol reaction. Main results were: 1) interaction between HRV and fat intake showing that HRV was positively associated with consumption of high-fat but had no effect on the consumption of low-fat, and 2) three-way interaction among cortisol, stress condition, and taste showing that in the stressful condition, cortisol was associated with an increased intake of sweet snacks while in the non-stressful condition, cortisol decreased the consumption of sweet foods. These results confirmed that the autonomic and endocrine responses contributed to explaining stress-induced food preferences, above and beyond the psychological variables.

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2-E-154 *microRNA and mRNA expression profiles reveal sexually dimorphic miRNA-gene regulatory networks in the mouse pituitary gland*

Cadia Chan[1], Huayun Hou[1], Liis Uuskula-Reimand[1], Dustin Sokolowski[1], Anna Roy[1], Kyoko Yuki[2], Matt Hudson[1], Mark Palmert[2], Zhaolei Zhang[1], Michael Wilson[2]

[1]University of Toronto, [2]The Hospital for Sick Children

It is known that activation of hypothalamic-pituitary-gonadal axis is crucial for puberty, however, the regulatory mechanisms behind pubertal initiation remains poorly understood. To discover miRNA-gene regulatory networks active during pubertal transition, 3'UTR-seq and small RNA-seq were performed to profile mRNA and miRNA expression across four ages spanning pubertal transition in mouse pituitary of both sexes. miRNAs with dynamically changing expression profiles across the ages were identified (n=37), two of which were found to have sexually dimorphic expression at the age of puberty. By incorporating mRNA expression profiles with validated and predicted gene targets we found negatively correlated gene targets that include known puberty-associated genes, transcription factors, and RNA-binding proteins with potential regulatory roles in miRNA biogenesis and RNA stability. In addition, these negatively correlated gene targets were enriched for gene ontology terms including response to hormone stimulus, tissue development, and neurogenesis. Overall, this study reveals candidate sex-biased miRNA-gene regulatory networks in the pituitary gland which may be important for pubertal development.

2-E-155 *The impact of the growth hormone secretagogue receptor in the ventral tegmental area on stress-induced feeding in mice*

Andrea Smith[1], Brenna MacAulay[1], Rebecca Prowse[1], Lindsay Hyland[1], Alfonso Abizaid[1]

[1]Carleton University

The peptide hormone ghrelin plays a role in regulating feeding behaviors, through its binding to the growth hormone secretagogue receptor (GHSR). In addition to stimulating appetite, ghrelin has also been implicated in regulating hedonic feeding and impacting an animal's response to stress. The ventral tegmental area (VTA) in the mesolimbic dopamine reward pathway displays relatively high expression of the GHSR, and these are expressed in dopaminergic neurons. Therefore, it has been hypothesized that ghrelin activation of neurons within the VTA also plays a critical role in regulating feeding behaviors, particularly following exposure to stress. To determine the significance of ghrelin signaling within the VTA in stress induced feeding, we reinstated expression of the GHSR in a line of transgenic male mice that only express the GHSR in the presence of cre-recombinase and exposed the animals to chronic social defeat stress. GHSR rescue in the VTA resulted in a significant increase in food intake in response to stress, compared to stressed GHSR KO controls and WT stressed animals. The results from our preliminary analysis provide strong evidence to suggest that GHSR expression within the VTA plays a vital role in

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regulating feeding behaviors in response to stress. This research provides evidence of a potential pathway by which ghrelin exerts its effects on the feeding response to chronic stressors.

F - Cognition and behavior

2-F-156 *Does neurogenesis predict hippocampus- and olfactory-dependent learning deficits in the goto-kakizaki rat?*

Alanna Chalk[1], Diano Marrone[1], Chelsey Damphousse[1], Nicole Micks[1], Jaclyn Medeiros[1], Josephine Esposto[1], Cassie Vivian[1], Nicholas Dosen[1]

[1]Wilfrid Laurier University

Research suggests that the chronic hyperglycemia associated with type 2 diabetes impairs brain function a number of ways - including a reduction in adult neurogenesis in the dentate gyrus and olfactory bulb. To investigate these impairments, Goto-Kakizaki (GK) rats were tested in both a radial arm maze and the social transmission of food preference (STFP), behaviours that depend on the integrity of the dentate gyrus and olfactory bulb, sites of profound adult neurogenesis. From the behavioural results obtained it is suggested that type 2 diabetes results in impairments to the dentate gyrus and olfactory bulb. Relative to age-matched Wistars, GKs demonstrated impairments in both behavioural tasks. On the radial arm maze, GKs showed increased latencies to complete the task, as well as increased errors. During STFP, GKs were unable to successfully discriminate between the flavoured foods provided to them, resulting in unsuccessful STFP. Using immunohistochemical procedures, doublecortin- and ki67- positive cells will be quantified to provide a measure of neurogenesis in these regions that can be compared with performance on these tasks. Together, these results will provide further information into the impairments associated with the presence of type 2 diabetes.

2-F-157 *An fMRI investigation of personal semantics*

Annick Tanguay[1], Daniela Palombo[2], Patrick Davidson[3], Louis Renoult[4]

[1]Rotman Research Institute, [2]University of British Columbia, [3]University of Ottawa, [4]University of East Anglia

Personal semantics are at the intersection of memory for culturally-shared facts (i.e., semantic memory) and memory for personal events (i.e., episodic memory; Renoult et al., 2012). That is, personal semantics resemble facts, but they relate to the self. Personal semantics are thought to vary in proximity to either semantic or episodic memory (Renoult et al., 2012). In this functional magnetic resonance imaging (fMRI) study, we investigated whether the neural correlates of autobiographical facts (AF; i.e., relatively objective facts about oneself) were closer to general

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facts/semantics (GF), and whether repeated events (RE; i.e., a summary of recurrent events) were closer to episodic/unique events (UE). We matched the stimuli across the four memory conditions, but varied their temporal orientation (present versus past) and specificity (from general to specific). Twenty-eight young adults participated. We focused on the hippocampus (HPC): The anterior HPC may be associated with memory for gist, whereas the posterior HPC may be related to memory for rich perceptual details. GF and AF did not differ from one another in anterior HPC, but differed in left posterior HPC. RE and UE did not differ from one another in any contrast. Activation increased gradually from GF to AF to RE and UE in the left posterior HPC. Thus, the data suggest that memory for "facts" (whether personal or not) share greater similarity with one another, and memory for "events" (whether unique or not) likewise. Overall, the data are coherent with a continuum perspective on personal semantics.

2-F-158 *Characterizing the activity of neural assemblies in the hippocampus across the full sleep-wake cycle*

Richard Boyce[1], Rosa Cossart[1]

[1]Inserm

Sequences of hippocampal place cells encode spatial trajectories as a subject navigates a given environment. During periods of restful wakefulness and non-REM sleep, condensed sequences corresponding to prior navigation recur during sharp-wave-ripple (SWR) events in the hippocampus, the disruption of which disturbs memory. Enabled by the use of large-scale neural imaging, recent work has revealed a more structured organization behind these sequences as they appear to be composed of multiple discrete assemblies connected together. Understanding this activity during various behavioral conditions and across different vigilance states is critical as assemblies may represent the basic unit upon which memories are encoded. However, the functional organization of the microcircuits, including assembly activity, recruited during REM sleep (REMs) remains unknown despite the recently confirmed role for REMs in the formation of spatial memory. To address this issue, we have employed large-scale 2-photon imaging in fully habituated head-fixed mice, enabling the simultaneous recording of hundreds of CA1 pyramidal neurons across multiple sleep-wake cycles, and under several tightly controlled experimental conditions (baseline in a cued / un-cued environment and following spatial learning in a cued environment). Cumulatively, these ongoing experiments provide a novel characterization of the recruitment and mechanistic role of neural assemblies in the hippocampus across the full sleep-wake cycle and under different environmental conditions.

2-F-159 *Study of memory and perceptual disorders in patients with Alzheimer's disease*

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Moussa Ahmadou Taher[1], Belahsen Mohammed Faouzi[2], Ahami Ahmed Omar Touhami[3]

[1]Laboratoire de Neurosciences Cognitivo-Comportementale et Nutrition appliquée, [2]Hassan II University Hospital, Fes, Morocco, [3]Cognitivo-Behavioral Neuroscience and Applied Nutrition Laboratory

Alzheimer's disease (AD) is a neurodegenerative disease, characterized by the gradual and irreversible weakening of cognitive functions such as memory, language, reasoning, and so on. The extension of brain damage causes other disorders that gradually reduce the autonomy of the person. It appears more often in the elderly, but it is not a normal consequence of aging. In order to better know the cognitive impairment screening bias, in non-familiar and non-verbal tests, Method and material The study was conducted at the Neurology Department of Hassan II University Hospital in Fez (Morocco). It included 20 Alzheimer patients from the Moroccan population. For the evaluation of the cognitive functions of the patients included in the study, we used the Rey type complex (FCR) A-type test. For the collection of plots, we used the method of Wallon and Mesmin, which consists in having the patient digitally plot on A4-size CREDAGE10 paper using an electronic "Anoto" system pen that records the dynamics of the lines as a sequence of x and y coordinates as well as instantaneous pressures. Chi (Pearson) and Student t tests were used to compare the variables. P value <0.05 is considered statistically significant. The data was analyzed with Excel and the SPSS Windows version 21 software.

2-F-160 *Chemogenetic excitation of ventral tegmental area dopamine neurons suppresses feeding but not responding to an alcohol conditioned stimulus*

Milan Valyear[1], Soraya Lahlou[1], Ghislaine Deyab[1], Alexa Brown[1], Nina Caporicci-Dinucci[1], Nadia Chaudhri[1]

[1]Concordia University

We found previously that responding triggered by a discrete alcohol-predictive conditioned stimulus (CS) was elevated in a context associated with alcohol intake, and that this elevation required activity in the dopaminergic projection from the ventral tegmental area (VTA) to the nucleus accumbens shell (NAcS). Here, we show that chemogenetic excitation of VTA dopamine neurons does not affect responding triggered by a discrete alcohol-predictive CS but attenuates feeding behaviour in the same animals. Male, transgenic TH::Cre rats received VTA microinfusions of a cre-dependent viral vector encoding the hM3Dq designer receptor. This receptor induces burst firing when bound by the ligands clozapine-n-oxide (CNO; 10 mg/kg i.p.) or clozapine (.1 mg/kg i.p.). Conditioned alcohol-seeking triggered by a discrete CS was unaffected by either ligand; however, consumption of standard chow was reduced by both ligands under conditions of mild food restriction. We further examined the role of VTA-to-NAcS excitation in TH::Cre rats by microinfusing the same hM3Dq construct in the VTA and implanting bilateral cannulae targeting

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the NAcS to deliver CNO (0 or 3 mM, .3 µl/hemisphere) before tests in which a discrete CS was presented in an alcohol or neutral context. Our pilot data indicate that activating the VTA-to-NAcS projection increased alcohol-seeking triggered by a discrete CS. Altogether, we show that broad activation of VTA dopamine neurons does not affect alcohol-seeking despite affecting feeding, but targeted excitation of VTA-to-NAcS neurons increases CS-triggered alcohol-seeking.

2-F-161 *Excitatory context conditioning promotes the reinstatement of appetitive Pavlovian conditioning*

Mandy LeCocq[1], Nadia Chaudhri[1]

[1]Concordia University

Context plays a dynamic role in the precipitation of relapse-like behaviours. Here, we examined the role of excitatory context conditioning in the reinstatement of responding to a sucrose-predictive cue. Rats (male, Long Evans, Charles River) received 12 Pavlovian conditioning sessions in which 8 presentations of a lever conditioned stimulus (CS; 20 s) each co-terminated with 0.3 mL of sucrose (10% w/v). Sucrose was delivered into a fluid port during the last 10 s of the CS (VT 280 s; 2.4 mL/session). Eight extinction sessions followed, in which the CS was presented without sucrose. Rats then received non-contingent exposure to sucrose in the fluid port, as during Pavlovian conditioning but without CS presentation. Next, separate groups received either 4 sessions of exposure to an alternate context, or 4 sessions of exposure to the context in which sucrose had been delivered, followed 24 h later by a reinstatement test in which the CS was presented without sucrose. A third group received this reinstatement test 24 h after non-contingent sucrose exposure. Prior exposure to sucrose reinstated CS port entries at test 24 h later, and at test following repeated exposure to the alternate context. However, reinstatement was significantly attenuated following repeated exposure to the context in which sucrose had been non-contingently delivered. This result suggests that an excitatory association between the context and sucrose is critical in driving reinstatement.

2-F-162 *Impact of ketamine on fear memory extinction and hippocampal reelin expression after corticosterone administration in rats*

Jenessa Johnston[1], Brian Kulyk[2], Raquel Romay-Tallon[1], Hector Caruncho[1], Lisa Kalynchuk[1]

[1]University of Victoria, [2]University of Saskatchewan

Chronic stress plays an important role in the pathogenesis of depression through prolonged elevated glucocorticoid levels which dysregulates glutamatergic signaling. As this is important in

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memory, patients with depression commonly display alterations in processing that biases the recollection of past events towards negative emotional information. Prolonged exposure to the glucocorticoid corticosterone (CORT) induces depression-like behaviour in rats, including making extinguished negatively-valenced associations more prone to reinstatement. This study investigated the effects of chronic CORT exposure on fear conditioning and extinction, and evaluated the efficacy of the ketamine in modulating fear and extinction recall in rats. The second aim was to determine ketamine's impact on reelin expression in the hippocampus. Reelin is a protein that induces similar neurobiological changes to ketamine, has been implicated in depression and glutamatergic signaling. Rats received 40 mg/kg of CORT for 21 days followed by a fear conditioning paradigm. 15mg/kg of ketamine was administered 60min prior to extinction training. Reelin expression was analyzed in the subgranular zone of the hippocampus. Regardless of prior CORT exposure, administration of ketamine induced a substantial attenuation of cue-elicited freezing during fear recall assessment. CORT administration decreased reelin expression, which was rescued by ketamine. The present study therefore establishes ketamine as a powerful modulator of fear memory, emotionally-driven behavior and a method of rescuing reelin expression.

2-F-163 *Episodic caching assists model free control in reinforcement learning tasks with changing reward contingencies*

Annik Carson[1], Blake Richards[2]

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

Biological agents learn to navigate a complex world in order to find food rewards - a non-trivial task involving parsing and correctly weighting contributions of task-relevant stimuli to the decision making process. Comptutational reinforcement learning (RL) models provide a normative framework in which to study the neural mechanisms for optimizing behaviour in reward tasks. Current RL model systems successfully solve stationary environments - i.e. where the underlying statistics remain stable over time - but fail when non-stationarity is introduced. It has been suggested that hippocampal-dependent rapid encoding of single episodes can provide a "one-shot" learning system that can be used to guide behaviour in the absence of up-to-date information about changes in environmental statistics. This has relatively low computational cost while maintaining flexibility in rapidly changing environments. We develop a model-free controller (MFC) with an auxiliary episodic caching (EC) system. We find that when underlying environmental statistics change, the MFC must relearn its policy at each state, but cached episodes in the EC can be used to formulate good policies for action selection. When MFC policies fail to produce rewarded actions, encouraging exploratory behaviour allowed the agent to cache novel experiences which ultimately led to finding the new reward state more quickly. Moreover, success

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with the EC system relies on principled choices about what episodes to store, with the greatest advantage conferred by storing episodes in which unexpected results were obtained.

2-F-164 *Depleting catecholamines impair motivation, but not cognition, in rhesus macaques*

Mavis Kusi[1], Martin Pare[1], Catherine Crandell[1]

[1]Queen's University

Catecholamines (CAT) are thought to significantly influence cognition. However, previous research in our lab found that increasing CAT (dopamine and norepinephrine) using reuptake inhibitors significantly improved motivation but only had marginal effects on working memory (WM) (Oemisch et al. 2016; Thurston et al. 2015). Here, we assessed if systemically depleting CAT using the acute tyrosine (TYR) phenylalanine (PHE) depletion (ATPD) method impairs WM and motivation. The ATPD method uses an amino acid mixture to deplete CAT via the depletion of their precursors TYR and PHE (Palmour et al., 1985). We first determined that the ATPD method reduces the concentrations of TYR and PHE in dried blood spots sampled from the animals' ear capillaries (Lefevre et al., 2015) by close to 90% three hours after mixture ingestion. We then assessed the effects of the ATPD mixture and a vehicle control mixture on WM using a visual sequential comparison (VSC) task and on motivation using a progressive ratio (PR) task. We also assessed task engagement (i.e. failure to complete or initiate trials) on the VSC task as a measure of motivation. For each animal, data from 5 ATPD sessions were compared to 5 vehicle control sessions as well as >60 no-vehicle control sessions. CAT depletion led to marginal and inconsistent changes in WM. However, it significantly impaired motivation as both animals significantly did worst on the PR task and on VSC task engagement after the ATPD mixture compared to vehicle control. Overall, our findings suggest that CAT play a more important role in motivation than WM.

2-F-165 *Investigating the cell type-specific roles of Npas4 in spine reorganisation during motor learning*

Pablo Serrano[1], Jungwoo Yang[1], Simon Chen[1]

[1]University of Ottawa

Motor skill learning requires repetitive training to acquire highly skilled and reproducible movements. This learning process has been shown to induce reorganisation of dendritic spines in pyramidal neurons (PNs) in the motor cortex (M1), and is tightly regulated by a specific subtype of inhibitory neuron, somatostatin interneurons (SOM-INs). However, it remains unclear how

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learning triggers differential signaling in each neuronal subtype, leading to subsequent learning-induced synaptic reorganisation. The activity-dependent transcription factor Npas4 is unique among others because its expression is induced in both excitatory and specific inhibitory neuron subtypes. More importantly, deletion of Npas4 in the CA3 region, but not CA1, of the hippocampus impairs contextual learning, suggesting an important role of Npas4 in regulating region- and cell-type specific genes that are involved for learning and memory. Preliminary data from our lab, using a head-fixed pellet-reaching task, revealed that the number of Npas4-expressing cells significantly increased in the trained mice. Interestingly, when we examined the cell-type identity, we found that learning-induced Npas4 expression predominantly occurs in PNs and SOM-Ins, but not in the other two major interneuron subtypes. To further investigate the cell-type specific roles of Npas4, we have utilized conditional Npas4 knockout mice (Npas4f/f) and CRISPR/Cas9 system, combined with in vivo two-photon imaging, to examine how learning-induced circuit reorganisations are affected during motor skill learning.

2-F-166 *Optogenetic activation of the infralimbic cortex to nucleus accumbens shell circuit attenuates the renewal of appetitive Pavlovian responding*

Franz Villaruel[1], Nadia Chaudhri[1]

[1]Concordia University

The infralimbic cortex (IL) is critical for inhibiting appetitive conditioned responses after extinction learning. We showed previously that activating the IL during a sucrose-predictive conditioned stimulus (CS) reduces context-induced renewal of Pavlovian responding. The IL is thought to exert its inhibitory control over appetitive responses through its neural projections to the nucleus accumbens shell (NAcS). In the present study, we predicted that activating the IL-NAcS circuit using optogenetics would suppress the return of appetitive Pavlovian responding in a context-induced renewal test. Male, Long-Evans rats received intra-IL viral injections of channelrhodopsin with enhanced yellow fluorescent protein (ChR2-eYFP) or eYFP alone, and were implanted with an optical fiber targeting the NAcS. Rats received Pavlovian conditioning in a distinct context (Context A) in which a CS (10 s white noise) was paired with the delivery of 10% sucrose in a fluid port. Next, rats received extinction in a different context (Context B) in which CS trials occurred without sucrose. Rats were then returned to Context A to induce renewal, and at test, optical stimulation was delivered in the absence of sucrose. Preliminary results indicate that activation of the IL-NAcS circuit during the CS but not during inter-CS intervals reduces the renewal of responding. Further, activating the IL-NAcS circuit in the extinction context did not affect responding. These results suggest that the IL-NAcS circuit is critical for suppressing the return of appetitive Pavlovian responding after extinction.

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2-F-167 *Transplanting immortal orexin cells in narcolepsy*

Sara Pintwala[1], Jennifer Chalmers[1], Jimmy Fraigne[1], Denise Belsham[1], John Peever[1]

[1]University of Toronto

Narcolepsy is a sleep disorder caused by loss of orexin neurons in the lateral hypothalamus. This results in symptoms such as excessive sleepiness and cataplexy, a sudden and involuntary loss of muscle tone during wake. The objective of cell transplantation is to treat disease by reinstating lost transmission. The aim of this study is to investigate a novel orexin cell line and to determine the outcome on behaviour by transplanting these cells in a mouse model of narcolepsy. To do this, we used an immortal cell line isolated from transgenic mice (m) expressing green fluorescent protein (GFP) in orexin (ORX) neurons, isolated from the adult (A) hypothalamus (Hypo), the mHypoA-ORX/GFP4 cell line. First, we performed immunocytochemistry against GFP and orexin. Then we performed a live cell secretion assay coupled with enzyme immunoassay. Next, we transplanted cells to the lateral hypothalamus (1.65/±1.0/4.5) in a mouse model of narcolepsy. The behaviour of transplant recipients were observed for cataplexy. All (100%) mHypoA/ORX-GFP4 (#cells=379; n=3) cells expressed orexin and GFP. Using a live cell assay we detected orexin secretion at baseline (0.276±0.030ng/ml; n=3; 5.0mM glucose media) with a significant increase in orexin release (0.337±0.031ng/ml; t-test; n=3; $p<0.01$) by a hypoglycemic challenge (0.2mM glucose media). In transplant recipients, there was a trend of reduced cataplexy episode number (12±1; mean±SEM; n=4) compared to controls (25±1; mean±SEM; n=2). This experiment highlights the potential of cell transplantation as a novel therapeutic strategy for narcolepsy

2-F-168 *Reduced functional interactions between the right entorhinal cortex and the posterior cingulate cortex in adults at risk for Alzheimers disease*

Gillian Coughlan[1], Peter Zhukovsky[2], Rachel Gillings[1], Vaisakh Puthusseryppady[1], Donnie Cameron[1], Michael Hornberger[1]

[1]Norwich Medical School, UEA, [2]Cambridge University

The development of clinically feasible, diagnostic tools for the detection of underlying preclinical Alzheimer's disease (AD) pathology relies on neuroimaging and biomarker research to improve diagnostic accuracy. Given that AD pathology first affects key nodes in the human navigation network, we hypothesised navigational changes would be present in adults at genetic risk to AD (APOE-e4 carriers) and that such changes can be explained on a neural level using functional magnetic resonance imaging methods. We found that 'at-risk' adults show reduced functional connectivity, specifically between the right entorhinal cortex (EC) and the posterior cingulate cortex (PCC), as well as an allocentric navigation bias toward environmental boundaries. We also show that this allocentric border bias is positively associated with reduced functional connectivity between the EC and PCC. Finally, we combined the observed navigational deficits and functional

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connectivity changes in a logistic regression to predict APOE genotype, achieving a classification rate of 83%. This provides evidence of behaviourally-relevant reduced regional connectivity in adults at genetic risk; 47% of whom will develop AD in the next decade.

2-F-169 *Neural correlates of extinction in a rat model of appetitive Pavlovian conditioning*

Alexa Brown[1], Franz Villaruel[1], Nadia Chaudhri[1]

[1]Concordia University

Inhibitory learning is fundamental for adapting to changing environmental contingencies. Extinction is a form of inhibitory learning; however, little is known about the neural correlates and networks that mediate the extinction of responding to appetitive cues. We used Fos expression to identify brain regions that were active following the extinction of responding to a sucrose-predictive cue. Briefly, male, Long-Evans rats received 8 daily, 57 min Pavlovian conditioning sessions, in which 10 trials of a CS (20 s white noise) occurred on a 280 s variable-time schedule. In the paired group, CS trials co-terminated with delivery of 10% sucrose (w/v) into a fluid port for oral consumption (0.3 mL/CS, over 10 s). Control groups also received CS presentations; however, sucrose was delivered either during the ITI or in the home-cage. After conditioning, 1, 2, or 6 extinction sessions were conducted wherein the CS was presented but sucrose was withheld. Thirty min after the end of the final extinction session, rats were deeply anesthetized, transcardially perfused, and their brains processed for c-Fos immunoreactivity. Preliminary data indicate that Fos expression in the infralimbic cortex (IL), but not the prelimbic cortex (PL), was elevated after one extinction session compared to 6 extinction sessions. These data suggest that the IL is implicated in extinction learning, and that it is more active in early extinction than late extinction.

2-F-170 *The effect of CCR5 antagonist Maraviroc in chronic oxycodone self-administration in rats.*

Catarina Borges[1], Nour Quteishat[1], Émilie Fortin[1], Vanessa Moman[1], Alexandra Chisholm[1], Craig Ferris[2], Uri Shalev[1]

[1]Concordia University, [2]Northeastern University College of Science

Oxycodone is a commonly abused opioid that significantly contributes to opioids-related deaths in the United States and Canada. Although it has been widely prescribed in the last 15 years mainly as a treatment for chronic pain, the neurobiological adaptations due to oxycodone chronic exposure are not fully understood. Recent evidence suggest that chronic self-administration of

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this mu opioid agonist can alter inflammation-related genes in dorsal and ventral striatum of adult mice, including the C-C-chemokine receptor type 5 (CCR5). We hypothesize that chronic exposure to oxycodone could lead to neuroinflammation via activation of CCR5. Consequently, blocking CCR5 receptor with an antagonist commonly used for HIV treatment, maraviroc, would reduce neuroinflammation and subsequently reduce self-administration. Using the Condition Place Preference (CPP) procedure, we found that rats injected with maraviroc prior oxycodone exposure did not develop preference for oxycodone-paired compartment. For our self-administration experiments, 12 rats will be trained to self-administered oxycodone (0.1 mg/kg/infusion) during 10 days. The effects of an acute treatment with maraviroc (10 mg/kg, IP) on the reinforcing properties of oxycodone and the motivation to take the drug will be tested under fixed ratio and progressive ratio of reinforcement. We expect to find a decrease in drug taking and in the motivation for oxycodone intake following treatment with maraviroc.

2-F-171 *Investigating the role of proteasome-mediated synaptic protein degradation underlying novelty-induced object memory destabilization in the perirhinal cortex*

Cassidy Wideman[1], Samantha Creighton[1], Kristen Jardine[1], Vino Thayalan[1], Krista Mitchnick[1], Bettina Kalisch[1], Boyer Winters[1]

[1]University of Guelph

The storage of long-term memory is more dynamic than once believed. The presentation of reminder cues can trigger consolidated long-term memories to destabilize, rendering them labile and necessitating protein synthesis-dependent reconsolidation. It has been postulated that the content of long-term memories can be updated when in this labile state. However, not all memories destabilize following reactivation. Our previous work has shown that novel contextual information at the time of reactivation can destabilize otherwise resistant object memories and that this process depends on proteasome activity in perirhinal cortex (PRh). Here we demonstrate that novelty-induced object memory destabilization is associated with reduction of post-synaptic density proteins (SHANK 3) in PRh, consistent with the notion of memory trace destabilization at the synaptic level. The ubiquitin proteasome system (UPS) regulates protein turnover and has previously been shown to mediate synaptic protein degradation following fear memory reactivation in the hippocampus. The current study aims to provide molecular evidence that the UPS is responsible for the synaptic protein reduction observed in PRh following object memory reactivation in the presence of explicit novelty. We are also currently investigating the molecular signals that activate the UPS in PRh following exposure to novelty, particularly CaMKII, which regulates proteasome activation for destabilization of other forms of memory. This work should thus clarify the molecular substrates of long-term object memory storage and modification.

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2-F-172 *Discovery of pharmacological approaches to selectively treat mood disorders caused by metabolic stress*

Thomas Horman[1], Matthew Scott[1], Francesco Leri[1]

[1]University of Guelph

Disorders characterized by dysfunctions in glucose metabolism are often comorbid with depression. The glucose antimetabolite 2-deoxy-D-glucose (2-DG) causes a stress response characterized by hypoglycemia and negative affect. The current project in laboratory animals is designed to investigate the impact of acute and repeated hypoglycemic stress on hedonic responses. In Experiment 1, male Sprague-Dawley rats were trained to self-administer the nutritional reinforcer high-fructose corn syrup (HFCS) via lever-pressing for an oral infusion for 14 days and then the effects of 2-DG (200 and 300 mg/kg; SC) were tested. In Experiment 2, 2-DG (200 and 300 mg/kg; SC) was injected immediately prior to acquisition of self-administration using progressive-ratio and fixed ratio schedules. Finally, Experiment 3 assessed whether 2-DG (200 and 300 mg/kg; SC) could alter appetitive oral-facial responses associated with HFCS using taste-reactivity. Experiment 1 demonstrated that 2-DG suppressed lever-pressing for HFCS for up to 6 days. Experiments 2 and 3 ruled out the possibility that this suppression was due to a context-induced malaise or to the development of taste aversion. These results suggest that hypoglycemia can induce a lasting anhedonic state characterized not only by negative affect, but also by impaired consummatory responses to incentive stimuli. We are currently exploring the consequences of chronic exposure to hypoglycemic stress on peripheral hormonal markers linked to nutritional rewards, as well as modulation of behavioral and physiological responses by antidepressants.

2-F-173 *Ventral hippocampal and amygdala interactions during context fear discrimination*

Robert Rozeske[1], Léonie Runtz[1], Aaron Sossin[1], Alexandra Keinath[1], Mark Brandon[1]

[1]McGill University

Assessing an environment as threatening or safe is critical for an organism's survival. Environments are encoded by the hippocampus via place cells whose firing is tuned to specific locations, which as a population form a cognitive map. Accordingly, numerous studies demonstrate the hippocampus is necessary to acquire context fear memories. Exactly how this hippocampal cognitive map interacts with amygdalar circuits to drive fear expression in threatening, but not safe, contexts remains largely uncharacterized. To understand whether the hippocampus differentially encodes these contexts we recorded calcium activity using fiber photometry in the ventral hippocampus (VH). Mice underwent context fear conditioning using a large cylindrical LED screen that permitted rapid alternation of multiple contexts. Presentation of

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shock-paired and non-shock paired contexts produced high and low levels of freezing, respectively. Transitions between threatening and safe contexts was associated with elevated VH calcium activity. One photon microendoscopy in the VH was adopted to investigate single cell calcium activity associated with context discrimination. Population analyses of place cell activity during context discrimination were performed to determine how these contexts are differentially represented. Together these studies demonstrate how cognitive maps in VH of threatening and safe environments are neuronally represented and potentially transmitted to downstream structures necessary for context fear discrimination.

2-F-174 *Successful decoding of sequence-specific duration information from human hippocampal long-term memory activity patterns*

Sathesan Thavabalasingam[1], Edward O'Neil[1], Jonathan Tay[1], Adrian Nestor[1], Andy Lee[1]

[1]University of Toronto

Our memories are rich with temporal information allowing us to remember 'when' a past event took place. The hippocampus (HPC) has been suggested to represent time in support of memory and rodent hippocampal time cells have been shown to signal the passage of time on the order of seconds between events. To explore whether a similar hippocampal mechanism exists in humans, participants first learned 4 distinct event sequences that varied in temporal structure (stimulus interval duration) and image content (scene identity) in a 2 x 2 factorial design. During functional MRI, participants were administered a recognition memory task for the learned sequences, as well as a recall task in which they mentally replayed each sequence in response to a cue. We found that individual sequences could be classified using activity patterns in anterior HPC during recognition memory and that successful classification could only be achieved through the combination of image content and temporal duration information that was unique to each sequence. A follow-up searchlight analysis revealed that the most informative voxels were in anterior CA1 and moreover, a classifier trained on anterior CA1 recognition data could successfully decode individual sequences from the mental replay data, suggesting that the same mnemonic representations underpinned both recognition and recall memory. Our findings align with rodent time cell research, and suggest that human hippocampal long term sequence memory representations can incorporate duration information on the order of seconds.

2-F-175 *Systemic injections of either L- or D-Lactate enhance retrograde, but not anterograde, inhibitory avoidance memory in young adult male Sprague-Dawley rats*

Claire Scavuzzo[1], Irina Rakotovao[1], Clayton Dickson[1]

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[1]University of Alberta

Ongoing activity-dependent processes, as well as brain metabolism, are important facets for learning and memory. Metabolic substrates like lactate are known to have influences for encoding and consolidating new memories as well as having influences on the production of state-dependent activity. L-lactate, a preferred neuronal energy substrate, enhances anterograde memory, while blockade of its uptake, pharmacologically or with D-lactate, impairs anterograde memory. Although metabolically inert, D-lactate can act like L-lactate by agonist action at the hydrocarboxylic acid receptor 1 (HCAR1), and can similarly induce deactivated, slow-wave activity. Deactivated patterns are beneficial for retrograde, but not anterograde, influences on memory. We tested signaling and metabolic effects of lactate on retrograde and anterograde memory using post- or pre-training treatments of L-lactate, D-lactate, and vehicle control in the inhibitory avoidance task. We found that post-training subcutaneous injections of L- or D-lactate (1 g/kg) significantly enhanced memory, suggesting that HCAR1 receptor-mediated mechanisms, not metabolism per se, underlie the retrograde benefits of lactate. Conversely, pre-training D- but not L-lactate, impaired memory compared to saline controls; suggesting that lactate metabolism alone is important for anterograde memory boosting. By monitoring EEG in the time frame after lactate manipulations we hope to dissect out influences of metabolism, HCAR-1 signaling, and brain state in memory modifications following lactate.

2-F-176 *A novel method of producing behavioural, genetic, and physiological changes from mild traumatic brain injury in mice*

Eric Eyolfson[1], Glenn Yamakawa[1], Richelle Mychasiuk[2], Alexander Lohman[1]

[1]University of Calgary, [2]Monash University

Traumatic Brain Injury (TBI) is one of the most common adolescent health issues with the vast majority of all TBI cases being mild (mTBI). The causes of mTBI include falls, automobile accidents, and sports injuries. Common post-concussive symptomology associated with mTBI include neuroanatomical modification, motor, and emotional behavioural deficits. Currently, models of mTBI in mice utilize either the fluid percussion model or the weight drop model. Here, we have developed a novel method of producing post-concussive symptomologies, the lateral impact model (LIM). LIM is a closed-head injury producing horizontal acceleration and rotation forces more typical in mTBI injuries. Forty-two male and female C57BL/6 mice were administered either single mTBI, repetitive mTBI, or sham injuries. All mice were tested on a behavioural battery to assess baseline locomotor activity, anxiety-like, and depressive-like tendencies. One day post-injury, mice received the same behavioural battery, with the addition of a motor balance test. In addition to these tests, we sought to assess physiological outcomes following LIM. qPCR was used to quantify telomere length and microglia and astrocytes were assessed for number and morphology by immunohistochemistry following mTBI. To our knowledge, we are the first to

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develop a lateral impact model of mTBI in the mouse which provides a more translational model to study concussions with employment of genetically modified animals and other experimental methods not currently available in larger model systems.

2-F-177 *Spatial memory formation requires netrin-1 expression by neurons in the adult mammalian brain*

Edwin Wong[1], Stephen Glasgow[1], Lianne Trigiani[1], Daryan Chitsaz[1], Vladimir Rymar[1], Abbas Sadikot[1], Edward Ruthazer[1], Edith Hamel[1], Timothy Kennedy[1]

[1]McGill University

Netrin-1 was initially characterized as an axon guidance molecule that is essential for normal embryonic neural development; however many types of neurons continue to express netrin-1 in the post-natal and adult mammalian brain. Netrin-1 and the netrin receptor DCC are both enriched at synapses. In the adult hippocampus, activity-dependent secretion of netrin-1 by neurons potentiates glutamatergic synapse function, and is critical for long-term potentiation, an experimental cellular model of learning and memory. Here, we assessed the impact of neuronal expression of netrin-1 in the adult brain on behavior using tests of learning and memory. We show that adult mice exhibit impaired spatial memory following conditional deletion of netrin-1 from glutamatergic neurons in the hippocampus and neocortex. Further, we provide evidence that mice with conditional deletion of netrin-1 do not display aberrant anxiety like phenotypes and show a reduction in self-grooming behaviour. These findings reveal a critical role for netrin-1 expressed by neurons in the regulation of spatial memory formation.

2-F-178 *The adaptor protein NCK1 is a regulator of anxiety-like behaviors*

Antonios Diab[1], Jiansong Qi[1], Crystal Milligan[1], James Fawcett[1]

[1]Dalhousie University

Anxiety is an adaptive response to a potential threat or stress. Anxiety disorder (AD) is characterized by changes in neuronal circuits that affect limbic system function and output. Although AD is considered to be heritable, specific genetic markers remain elusive. Here we examined the role for the adaptor protein NCK1, a protein implicated in actin dynamics, in regulating anxiety-like behaviours. Although no deficits in sensory and motor outputs were detected, mice lacking NCK1 displayed more anxiety-like behaviours. Further, NCK1-/- mice showed higher levels of circulating corticosterone following behavioural testing. Since the prefrontal cortex (PFC) - basolateral amygdala (BLA) axis has been closely associated with anxiety, we further investigated these brain regions in our mutant mice. Loss of NCK1 did not

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affect the development of these regions, nor did it affect axonal targeting into the amygdala. However, mice lacking NCK1 showed decreased dendritic spine density within the BLA. These changes in synaptic density were reflected in an overall decrease in activation of PFC neurons, and a reduction in the activity of inhibitory interneurons within the BLA. Finally, pharmacological treatment with the anxiolytic diazepam rescued the anxiety phenotype. Taken together, our data suggests that NCK1 functions in the development of the PFC/BLA axis by maintaining appropriate excitatory/inhibitory balance within the limbic system to regulate anxiety. Further, we suggest that mice lacking NCK1 provide a unique animal model for understanding anxiety behaviors.

2-F-179 *Effects of estrogen depletion, age, and functional brain activity on associative memory in spontaneous menopause and surgically-induced menopause*

Alana Brown[1], Anne Almey[1], Nicole Gervais[1], Annie Duchesne[2], Laura Gravelsins[1], Elizabeth Baker-Sullivan[1], Daniel Nichol[3], Giulia Baracchini[3], Cheryl Grady[4], Gillian Einstein[1]

[1]University of Toronto, [2]University of Northern British Columbia, [3]Rotman Research Institute, Baycrest Health Sciences, [4]University of Toronto and Rotman Research Institute, Baycrest Health Sciences

Surgical removal of the ovaries via bilateral salpingo-oophorectomy (BSO) prior to spontaneous menopause (SM) is correlated with increased Alzheimer's disease (AD) risk. The objective of this study is to clarify the distinct roles of estrogen loss and age on memory and functional brain activity in the anterior hippocampus (aHPC) and frontoparietal attention network during associative encoding. Paired associative learning deficits are considered the earliest and most salient AD symptoms, heralding preclinical AD. There is little understanding of the influence of depletion of a potent estrogen, 17β-estradiol (E2), on associative memory following BSO. We administered a face-name associative memory task that is sensitive to prodromal AD. Using fMRI, we assessed brain activity during face-name pair encoding and compared recognition performance of women who underwent BSO to that of age-matched premenopausal control (AMC) and SM women. SM was associated with the lowest recognition accuracy compared to BSO and AMC ($p < .05$). SM and BSO women (not taking E2-based hormone therapy) had comparable circulating E2 levels, and BSO women were, on average, 11 years younger than SM women, suggesting that age affects associative ability more strongly than E2 loss. fMRI results clarify the distinct impacts of BSO and SM on activity in the aHPC, amygdala, and prefrontal and parietal cortices during encoding. Understanding functional activity variations between these groups during associative learning is critical for distinguishing memory effects resulting from normal aging versus E2 loss.

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2-F-180 *Behavioural characterization of the Nrxn1+/- mouse model of autism spectrum disorder*

Qendresa Sahiti[1], Spencer Brown[1], Richard Brown[1]

[1]Dalhousie University

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by deficits in social interaction, increased repetitive and stereotypical behaviours, and abnormal responses to sensory stimulation. Previous research has linked the causation of ASD to complex gene-environment interactions, which are not fully understood. Neurobiologically, ASD has been associated with abnormalities in synaptic connectivity in the brain, and mutations in the neurexin cell adhesion protein family have been identified in individuals with ASD. The Nrxn1+/- mouse is a novel knock-out model of ASD that carries only one functional allele of neurexin 1. The behavioural phenotype of this mouse is unknown and knowledge of the behavioural phenotype is essential because the diagnosis of ASD is based on behavioural symptoms. In this study we tested 20 Nrxn1+/- mice (10M, 10F) and 20 C57BL/6J wild-type control mice (10M, 10F) at two months of age in a behavioural test battery. This included 16 tasks that evaluated cognitive and motor performance, mood and anxiety, stereotypical behaviour, social interaction, and visual ability. While the Nrxn1+/- mice showed no cognitive or social deficits compared to the wild-type mice, they performed worse on some motor tests and showed increased levels of anxiety. These preliminary results give some indication of the behavioural effects of the expression of neurexin 1. We are currently extending our test battery and testing mice at other ages to determine if they show age-related changes in their behavioural phenotype.

2-F-181 *Norepinephrine in auditory processing areas enhances the developmental learning of communication signals*

Sarah Woolley[1], Jon Sakata[1], Yining Chen[1]

[1]McGill University

Sensory learning, specifically auditory learning, serves as the foundation for vocal learning and imitation. Catecholamines such as norepinephrine (NE) have been implicated in various forms of sensory processing but the extent to which they contribute to auditory learning for vocal learning remains largely unknown. Like humans, songbirds acquire their vocal communication signals ('songs') during development. Our recent studies implicate NE in vocal learning because NE-synthesizing neurons in the locus coeruleus express more immediate early genes under conditions that promote song learning (Chen, Matheson, and Sakata, 2016). To investigate how NE in the avian analogue of the secondary auditory cortex impacted sensory song learning in juvenile zebra finches, we infused NE or vehicle into the secondary auditory cortex of naïve juvenile zebra finches (i.e., birds that were not previously tutored) as they were briefly tutored with

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song. We found that birds given NE produced more accurate imitations of their tutor's songs as adults. In a second experiment, we found that administering NE promoted the learning of additional vocal elements when experienced juvenile birds (i.e., birds that have already learned a song) were tutored with a second tutor's song. We also observed rapid manifestations of vocal learning following NE administration. Taken together, our data indicate that NE can act within auditory processing areas to rapidly promote the developmental acquisition of communication signals.

2-F-182 *A novel 'enrichment track' protocol produces enhanced cognitive benefits compared with traditional home cage enrichment in mice*

Heather Collett[1], Sandra Gattas[2], Ethan Huff[1], Samantha Creighton[1], Shoshana Buckhalter[1], Siobhon-Elora Weber[1], Silas Manning[1], Bruce McNaughton[3], Boyer Winters[1]

[1]University of Guelph, [2]University of California, Irvine, [3]Lethbridge University

Environmental enrichment (EE) protocols for rodents vary widely, but consistently fail to allow for fine measurement or control of the quantity and quality of individual animal enrichment. Here we present a novel enrichment protocol that addresses these limitations by exposing mice to enrichment outside of their home cage on a running track filled with obstacles. This protocol increases the amount of complexity and novelty each animal experiences by motivating them to explore and problem-solve to achieve a small milkshake reward for each lap completed in daily 1-hour sessions (6 day/week) on the enrichment track. The number and duration of daily laps can be quantified for comparison and control between mice. To validate this method, 28 day-old male C57/BL6 mice were assigned to four experimental groups (n = 10/group): home cage enrichment (EE); enrichment track (ET); exercise control track (CT); or standard ("impoverished") housing control (SH). The ET and CT groups were also housed the same as the SH group. Following two months in these conditions, memory performance was assessed using a 'difficult' version of the object recognition task with reduced sample exploration. Although there was evidence for cognitive enhancement in both the EE and ET groups with a 20-min retention delay, only the ET mice discriminated between familiar and novel objects with a 24-h delay. Thus, the novel ET method represents an important advance over typical home cage enrichment protocols as it enables more direct and measurable individual enrichment and may produce greater cognitive benefits.

2-F-183 *Extinction and reinstatement of cue-based reward-seeking after chemogenetic activation of VTA-GABA neurons*

Justin McGraw[1], Sondos Al-Khaledi[1], Martin Leigh[2], Ken Wakabayashi[1], Malte Feja[3], Caroline Bass[2]

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[1]University at Buffalo, [2]SUNY at Buffalo, [3]University of Veterinary Medicine Hannover

Reward-predictive cues may incentivize reward-seeking. The role of VTA-GABA neurons in regulating cue-induced responding has recently been investigated. Our laboratory has shown that chemogenetic activation of VTA-GABA neurons attenuates operant responding to cues that predict a highly palatable reward (10% sucrose). Yet, when the terminals of VTA-GABA neurons are activated in the nucleus accumbens (NAc), there are no changes in responding, indicating that VTA-GABA interneurons and projection neurons to the NAc mediate different aspects of motivation. Indeed, we show that GABA projections enhance adaptation when the predictive value of the cue is altered by decreasing reward magnitude. In this study, we examined the robustness of adaptive motivation for the cue in an extinction and reinstatement design after chemogenetic activation of VTA-GABA projections to the NAc. We used a combinatorial viral vector approach to restrict activating Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) to GABA neurons in the VTA of male Long-Evans rats trained to respond in an operant task of incentivized cue responding. Multiple dependent measures of reward choice and vigor of responding are obtained, and we compare these to standard metrics of motivation (e.g., progressive ratio) and consumption (e.g., fixed ratio). Our preliminary results indicate that activation of VTA-GABA terminals enhances the speed with which rats adapt their responding to cues when the reward magnitude is altered from their previously learned cue-reward association.

2-F-184 *Behavioral effects of long-term, high-dose nicotine exposure during adolescence in rats*

Cassandra Sgarbossa[1], Jude Frie[1], Allyson Andrade[1], Briana Renda[1], Joshua Smit[1], Lauren King[1], Samantha Creighton[1], Boyer Winters[1], Jennifer Murray[1], Jibran Khokhar[1]

[1]University of Guelph

Adolescent nicotine exposure is an increasing concern with the emergence of electronic cigarette devices (e.g. vaping), highlighting the importance of considering long-term behavioral consequences of adolescent exposure. Male Sprague-Dawley rats (n=16, 8/group) were treated daily with 1.0 mg/kg subcutaneous nicotine from post-natal days 28-42. Upon adulthood, rats underwent behavioral assessments: object recognition memory, conditioned avoidance response (CAR), and intravenous nicotine self-administration. Adolescent nicotine-treated rats displayed a significant, but selective, impairment of short-term memory (5-minute delay). A significant within-animal delay by drug interaction ($F(1,14)=4.748$, $p=0.047$) was observed; between-group analyses showed that nicotine-treated animals displayed significantly decreased discrimination ratio compared to vehicle-treated animals ($p=0.011$). No group differences were observed in acquisition or extinction of CAR. For nicotine self-administration (0.023 mg/kg/infusion), there was no effect of nicotine pretreatment on a fixed ratio 1 schedule. However, during a fixed interval 1 schedule, rats pretreated with nicotine self-administered nicotine more than rats not pretreated

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with nicotine, [Session x Group Interaction: F(7,70)=2.403, p=.029]. Adolescent exposure to high-dose nicotine produces long-lasting changes in short-term memory and nicotine reinforcement, underscoring the need for understanding the long-term consequences of nicotine use in adolescence.

2-F-185 *The effect of chemogenetic modulation of cortico-thalamic projections in the augmentation of heroin seeking induced by chronic food restriction*

Alexandra Chisholm[1], Émilie Fortin[1], Vanessa Moman[1], Damaris Rizzo[1], Jean-Philippe Manoliadis[1], Nour Quteishat[1], Uri Shalev[1]

[1]Concordia University

Chronic food-restriction results in augmented drug seeking in abstinent rats, compared to sated rats. We have previously shown that chemogenetic activation of the paraventricular nucleus of the thalamus (PVT) reduces heroin seeking in food-restricted animals. A major excitatory input to the PVT is from the medial prefrontal cortex (mPFC). Thus, the objective of the current study was to study the effect of chemogenetic activation of the mPFC-PVT neuronal pathway on heroin seeking under food restriction conditions. Male Long Evans rats were injected with a viral vector carrying an excitatory Designer Receptor Exclusively Activated by Designer Drug (DREADD) into the mPFC, and implanted with a guide cannula aimed at the PVT. Next, rats were trained to self-administer heroin over the course of 10 days (0.1 mg/kg/infusion; i.v.). Following training, rats were removed from the operant conditioning chambers and placed into drug withdrawal for 15 days. Over the withdrawal period, rats were exposed to a mild food restriction (90% of baseline body weight) or were given unrestricted access to food. On the 15th day of the withdrawal period, a drug-seeking test was conducted in which rats were intracranially injected with CNO (1.0 mM) into the PVT, to excite the mPFC-PVT afferent terminals, or vehicle. As expected, food-restricted rats demonstrated an augmented heroin seeking during the heroin-seeking test in comparison to sated rats. Preliminary results suggest that chemogenetic activation of the mPFC-PVT pathway does not attenuate heroin seeking in food-restricted or sated rats.

2-F-186 *Enhancement of memory consolidation by cocaine, nicotine, and their conditioned contexts may be mediated by a common noradrenergic mechanism*

Michael Wolter[1], Talia Speigal[1], Boyer Winters[1], Francesco Leri[1]

[1]University of Guelph

Cocaine, nicotine and contextual stimuli (CS) associated with their effects enhance memory consolidation. These drugs also enhance monoamine transmission in several memory systems.

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Our parallel findings with cocaine, nicotine and their CSs suggest that the effects of these drugs and their CSs may facilitate memory storage by activating overlapping neurobiological systems during memory consolidation. One system likely to be involved in the acute effects of such drugs, as well as exposure to their CSs, is noradrenaline (NA) because of its roles in drug reinforcement and memory enhancement produced by emotional stimuli. The current study tested this hypothesis in male Sprague-Dawley rats performing an object recognition memory task. The CSs were generated using a within-subjects conditioning protocol to produce a drug-conditioned context (CS+) and a vehicle-conditioned context (CS-). Post-sample injections of cocaine (20 mg/kg) or nicotine (0.4 mg/kg) enhanced object recognition memory, and these effects were impaired by co-administration of the β-noradrenergic receptor antagonist propranolol (5 and 10 mg/kg). More interestingly, the previously reported memory enhancing effects of post-sample exposure to the cocaine or nicotine CS+ was also blocked by propranolol (10 mg/kg). Overall, these data suggest that cocaine, nicotine and their CSs promote object memory consolidation by enhancing noradrenergic transmission, indicating a neurochemical function of adrenergic tone that may impact the persistence and maintenance of addictive behaviours. Supported by NSERC.

2-F-187 *Does sex moderate the relationship between prudent diet consumption and cognition in late life?: Findings from the NuAge study*

Danielle D'Amico[1], Matthew Parrott[2], Carol Greenwood[3], Guylaine Ferland[4], Pierrette Gaudreau[4], Sylvie Belleville[4], Danielle Laurin[5], Nicole Anderson[3], Bryna Shatenstein[4], Marie-Jeanne Kergoat[4], Jose Morais[6], Alexandra Fiocco[1]

[1]Ryerson University, [2]Concordia University, [3]University of Toronto, [4]Université de Montréal, [5]Université Laval, [6]McGill University

Growing evidence suggests that consumption of an nutrient-rich prudent diet high in fruits, vegetables, lean meats, nuts, and seeds is associated with enhanced cognitive performance in older adulthood. Although sex differences in the relationship between certain dietary components and cognition have been observed, there is a paucity of research that examines sex as a potential effect-modifier in the diet pattern-cognition relationship. The current study investigated the moderating role of sex in the relationship between prudent diet intake and global cognitive function at baseline in 1294 community-dwelling older adults free of cognitive impairment (Mage=74.3±4.2, 52.7% female) from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge). A Food Frequency Questionnaire was used to estimate dietary intake. Principal component analysis was conducted to derive prudent diet pattern scores. Global cognition was assessed using the Modified Mini-Mental Status examination. Moderation analyses using linear regression revealed no significant diet x sex interaction, indicating no difference between men and women in the relationship between prudent diet pattern and cognition. Controlling for age, education (< high school, > high school), hypertension, and usual daily energy intake, higher

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prudent diet was associated with better global cognition (B=.47, p<.001, 95% CI [.222, .718]). Confirming the benefits of a nutrient-rich diet pattern for cognitive function in late life, this study further suggests that the benefits are not sex-dependent.

2-F-188 *The behavioural effects of lipopolysaccharide in adolescent male and female rats*

Indra Bishnoi[1], Martin Kavaliers[1], Klaus-Peter Ossenkopp[1]

[1]University of Western Ontario

There is accumulating evidence for sex differences in the behavioural, physiological, and immunological effects of infection. Lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria, such as E. coli and Salmonella, has been effectively used to examine these differences. Generally, males are more susceptible to infection than females. Age-related changes are a contributing factor to this sex difference. There have been limited investigations of: (1) the impact of infection during the adolescent period, (2) the long-term effects in later adolescence compared to adulthood, and (3) whether or not there are sex differences in these long-term effects. As such, the current study is examining sex differences in the long-term effects of LPS measured in late adolescence and adulthood following early adolescent LPS exposure. Sixteen rats were assigned to each of the LPS (0.2 mg/kg dissolved in 0.9% NaCl) and vehicle control (0.9% NaCl) groups and received intraperitoneal injections in early adolescence on postnatal day 30 and 32. After a five-day washout period, this study examined: (1) general locomotor activity; (2) anxiety; (3) social behaviour; (4) cognitive ability, i.e. memory; and (5) sensorimotor gating. Initial findings within adolescent male rats show that LPS increased locomotor activity levels but failed to elicit anxiogenic effects and sensorimotor gating deficits.

2-F-189 *Adult neurogenesis mediates forgetting in the rat*

Kelsea Gorzo[1], Jonathan Epp[1]

[1]Hotchkiss Brain Institute

The formation and retention of hippocampus dependent memories is impacted by adult neurogenesis, a process which involves the production of new neurons in the dentate gyrus of the hippocampus. This region is important for many types of learning and memory. Furthermore, these new neurons are believed to influence memories in a unique manner. Recent studies have demonstrated that increasing neurogenesis after memory formation induces forgetting of these previous memories. These findings suggest that neurogenesis promotes forgetting to reduce interference between multiple similar memories. Neurogenesis induced forgetting was originally

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demonstrated in mice but a recent report suggests that the same effect is absent in rats. A potential explanation for these incongruent findings is that memories which are more strongly reinforced become resilient to forgetting. Here, we investigated whether neurogenesis induced forgetting occurs in rats and whether stronger memories are less susceptible to forgetting compared to others. Rats were trained on several hippocampal dependent memory tasks and split into strong training and weak training groups to assess different memory strengths. Neurogenesis was then increased using natural and pharmacological means for 4 weeks before recall of the previous memory was assessed. We show here that regardless of strength of training, memories were susceptible to neurogenesis induced forgetting in rats. These results suggest that forgetting due to neurogenesis is a conserved mechanism that optimizes neural circuity for the encoding of new memories.

2-F-190 *Effects of MAGL inhibition on free intake of sucrose and effort-based decision-making*

Sondos Al-Khaledi[1], Justin McGraw[1], Martin Leigh[2], Kimberly Bernosky-Smith[3], Ken Wakabayashi[1], Malte Feja[4], Caroline Bass[2]

[1]University at Buffalo, [2]SUNY at Buffalo, [3]D'Youville College, [4]University of Veterinary Medicine Hannover

Endocannabinoid (eCB) signaling and its effect on dopamine neurotransmission and reward seeking behaviors has seen increasing interest in recent years. The eCB system presumably can modulate these behaviors due to the dense distribution of CB1 receptors within the mesocortical areas, such as the NAc and PFC. Enhancement of the eCB 2-arachidonyl glycerol (2-AG), by MJN110, which inhibits its degradatory enzyme monacyl glycerol lipase (MAGL), increases responding to reward predictive cues. Studies have also suggested that CB1 agonism increases appetite and the value of reward associated with food. However, others have shown that eCBs, and specifically MJN110, can produce an anoretic effect. We sought to clarify the effect of MAGL inhibition on motivation and consumption of a hedonic food. Male Long Evans rats were tested in a free-drinking task measuring consumption of a 10% sucrose solution. Pretreatment with MJN110 (10mg/kg i.p.) increased cumulative consumption compared to vehicle conditions, with no change in consumption early in the session (~5-7 ml). Additionally, to elucidate the effects of MAGL inhibition on decision making processes, we subjected rats to a T-maze where they perform a cost-benefit decision on whether to opt for the arm with a barrier and a large reward or the arm with no barrier and a small reward. Collectively, our results suggest that the elevated operant response for sucrose consumption is likely a result of a change in the motivational processes rather than a change in appetite alone.

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2-F-191 *Heterogeneous contribution of endocannabinoids to cue-induced reward seeking in the Nucleus accumbens and ventral tegmental area.*

Martin Leigh[1], Malte Feja[2], Ajay Baindur[1], Wakabayashi Ken[1], Micah Niphakis[3], Ben Cravatt[4], Caroline Bass[1]

[1]SUNY at Buffalo, [2]University of Veterinary Medicine Hannover, [3]Abide Therapeutics, [4]The Skaggs Institute for Chemical Biology

The endocannabinoids (eCBs) 2-arachidonoyl glycerol (2-AG) and anandamide (AEA) are metabolized by the enzymes monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively. Using an operant task, in which rats nosepoke during discrete audiovisual, incentive cues (ICs) for 64µl of 10% sucrose, we demonstrated that antagonizing eCB tone at the CB1 receptor decreases responding to ICs. To capture decreases in responding we developed a task variant, in which the reward progressively decreases every 15 mins (64µl, 48µl, 32µl, 16µl). The choice and vigor to respond to ICs decreases proportionately with the volume of sucrose delivered. MAGL inhibition with MJN110 (i.p.) enhanced both the choice and vigor of responding to ICs. Our current study sought to define brains responsible for these effects by microinfusing the compounds directly into the VTA and NAc. Additionally, we tested a FAAH inhibitor PF3845 to determine AEA's contribution to reward-seeking. MJN110 (2µg, 4µg), rimonabant (3µg), PF3845 (4µg) were microinfused into the VTA or NAc of male Long Evans rats. Intracranial MAGL inhibition enhanced responding to the ICs, and decreased the latencies to respond and obtain the reward. However, rimonabant and PF3845 affected responding when injected in the NAc, but not the VTA. Our results suggest 2-AG levels regulate responding in the VTA to reward predictive incentive cues, while both 2-AG and AEA regulate NAc influences on cue-induced reward-seeking. Together our data demonstrates heterogeneous regulation of reward seeking by eCBs in mesoaccumbal circuits.

2-F-192 *A large-scale spiking neuron model of the neurobiology underlying innate defensive behaviors*

Kathryn Simone[1], Nuria Daviu Abant[1], Kartikeya Murari[1], Jaideep Bains[2]

[1]University of Calgary, [2]Hotchkiss Brain Institute

All animals have evolved repertoires of innate behaviors for predator defense. The hypothalamus is critical to a number of innate behaviors including defense. Coordinated activity across several nuclei is thought to contribute to these behaviors, but exactly when and how those contributions are made is not clear. One limitation to advancing knowledge is that there are no computational models describing innate defensive behaviors in rodents. In order to address this knowledge gap, we developed a large-scale spiking neuron model for the neurobiological basis of innate defensive behaviors in response to looming and advancing visual stimuli. The model was developed through

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application of the Neural Engineering Framework to integrate functional and mechanistic constraints from published data, capturing a hypothesized architecture and dynamic interactions that may underlie the generation of specific behaviors and their organization in time. We then extend this framework to incorporate key findings from our lab: that anticipatory activation of corticotropin-releasing hormone neurons in the paraventricular nucleus is required for active avoidance behavior of aerial threats (unpublished results), and that stress controllability training alters their activity and the expression of active avoidance behavior. The model's predictive value is assessed against its ability to reproduce physiological and/or behavioral datasets that we're not used to create the model. The model makes specific predictions that motivate further experimental investigation.

2-F-193 *Short and Long-Term Effects of Adolescent Cannabis and Alcohol Co-Use*

Shahnaza Hamidullah[1], Claudia Lutelmowski[1], Jibran Khokhar[1]

[1]University of Guelph

BACKGROUND: Cannabis and alcohol co-use is prevalent in adolescence but its long-term effects on learning and cognition remain largely unexplored. Therefore, the aim of this study is to investigate the effects of adolescent alcohol and Δ9-tetrahydrocannabinol (THC) co-exposure on learning and cognition. We hypothesize that co-exposure will produce more pronounced behavioral and cognitive deficits in adulthood compared to either drug exposure alone. METHODS: Male Sprague Dawley rats received vapourized THC (10 mg/pad) or vehicle every other day and had continuous access to 10% ethanol in a two-bottle choice design during adolescence (post-natal day 28-42). Alcohol intake was measured during the exposure period to assess the acute effects of THC on alcohol consumption. In adulthood, a battery of behavioural tests (i.e., novel object preference, elevated plus maze, conditioned avoidance response, and autoshaping) was performed. RESULTS: Adolescent rats showed higher alcohol preference and consumption on days in which they were not exposed to THC vapour. In adulthood, co-exposed animals trended towards better short-and-long-term memory retention on the novel object preference compared to those that received either drug alone. In the conditioned avoidance response test, those exposed to THC alone exhibited higher resistance to extinction compared to co-exposed and alcohol-exposed animals. CONCLUSION: These results contrast our previous findings with injected THC exposure, suggesting that different routes of administration can produce varying short- and long-term consequences

2-F-194 *Impact of early estrogen deprivation on sleep quality and hippocampal volume in middle-aged women: preliminary findings*

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Nicole Gervais[1], Gina Nicoll[1], Elizabeth Baker-Sullivan[1], Leanne Mendoza[1], Claire Lauzon[1], Anne Almey[1], Laura Gravelsins[1], Alana Brown[1], Annie Duchesne[2], Rosanna Olsen[1], Cheryl Grady[3], Gillian Einstein[1]

[1]University of Toronto, [2]University of Northern British Columbia, [3]University of Toronto and Rotman Research Institute, Baycrest Health Sciences

Sleep plays an essential role in promoting memory and hippocampal (HPC) structural integrity. Hormone deprivation following menopause is associated with increased sleep and memory complaints; estradiol-based hormone therapy (ET) improves symptoms, and increases HPC volume. Early surgical menopause (via bilateral salpingo-oophorectomy, BSO) is associated with greater risk of sleep disturbance (SD) relative to natural (i.e spontaneous) menopause. Unknown are whether menopause-associated SD contributes to HPC atrophy, and whether ET use and early BSO influence this relation. Our study aimed to determine whether: 1) early hormone deprivation (via BSO) leads to greater SD and HPC atrophy, 2) ET ameliorates changes, and 3) menopause-associated SD relates to HPC subfield volumes. Women aged 36-60 were recruited as either BSO on ET (BSO ET) or not on ET users (BSO), spontaneously menopausal (SM), or premenopausal age-matched controls (AMC). Structural scans were obtained and volumes of HPC subfields were quantified manually using high-resolution T2-weighted scans. Subjective and physiological sleep measures were collected. Preliminary results indicate reduced volume in the dentate gyrus, CA2 and CA3 subfields (DGCA23), and SD in the BSO and SM groups, with amelioration in BSO with ET use. There were no differences between the BSO and SM groups. Sleep quality correlated negatively with DGCA23 volume. This study underscores the adverse effects of early estradiol loss on sleep and HPC integrity, and suggests that menopause-associated SD may contribute to HPC atrophy.

2-F-195 *Evaluating mindfulness-induced cognitive changes: Scope for improving inhibitory control in young adults*

Varsha Singh[1], Vaishali Mutreja[1]

[1]Indian Institute of Technology, Delhi

Objective: Evaluating mindfulness-induced benefits in executive control in young adults, and accounting for ceiling/practice effect. Method: A pre-post comparison (N=54) of executive control of 27 participants (mean:22.5 yrs.) who received 8-weeks mindfulness training (bi-weekly yoga & pranayama: 30 min each) and age-gender matched controls (n=27). Material: Accuracy and RT were analyzed for executive control components: working memory (DS, Corsi, MRT), planning/flexibility (ToH, ToL, BCST), inhibition (Simon, Stroop, IGT). Four tasks were repeated (pre, post-mindfulness) and 5 tasks were non-repeated (post-mindfulness). Result: Mixed ANOVA used for within-group differences (repeated tasks) showed the interaction of time × group

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suggesting improved working memory (DS task) in the mindfulness group (p<.05). Between-group comparison (five tasks) showed that mindfulness group had high accuracy (p<.05) and short RT (p<.05) in inhibitory control (Stroop task). Conclusion: Studies of mindfulness-induced cognitive benefits should address 'ceiling/practice effects' by comparing repeated and non-repeated tasks. For example, results for the repeated tasks suggests mindfulness-induced selective malleability of working memory and significant difference in inhibitory control for the non-repeated tasks. Lack of inhibitory control and increased risk behavior is characteristic of young adulthood - mindfulness might enhance inhibitory control, possibly by improving working memory.

2-F-196 *Synthetic estrogen and cognition: Do time of oral contraceptive ingestion and the COMT Val158Met polymorphism affect working memory?*

Laura Gravelsins[1], Ava Ma de Sousa[1], Clara McNamee[1], Karla Machlab[1], Pascale Tsai[1], Brittany Demircan[1], Leah Velikonja[1], Katherine Duncan[1], Gillian Einstein[1]

[1]University of Toronto

The main estrogen produced by the ovaries, 17-beta estradiol (E2), plays a key role in memory. Whether synthetic estrogens in oral contraceptives (OCs) play the same role is largely unknown. One major difference between OCs and endogenous E2 is that plasma concentrations of ethinylestradiol (EE), the main synthetic estrogen in OCs, typically peak 1-2 hours after pill ingestion, leaving OC users with low levels of EE and E2 before their next dose. We asked how the pharmacokinetics of EE might affect working memory (WM) in OC users as compared to normally cycling (NC) controls. Controlling for time of day, we tested OC users at a peak EE state 1-2 hours after pill ingestion, and at a low EE state just before pill ingestion. NC controls were tested at low and high E2 menstrual cycle phases. Participants were also genotyped for the catechol-o-methyltransferase (COMT) gene, which codes for an enzyme that degrades cortical dopamine (DA), to determine whether OCs interact with different DA availabilities due to the COMT Val158Met polymorphism to modulate memory. Previous research has shown E2 interacts with this polymorphism to regulate WM, so we wondered if EE does the same. Our results showed that time since pill ingestion did not affect WM performance, there was no difference in WM performance between the COMT genetic variants, and no interactions with genotype and time of pill ingestion. These data suggest that despite the concentration variability of EE in OC users within a 24-hour period and the variability of DA breakdown, women on OCs have stable WM throughout the day.

2-F-197 *Hemispheric differences in functional interaction between dorsal lateral prefrontal cortex and ipsilateral motor cortex*

Yanqiu Wang[1], Na Cao[1], Robert Chen[2], Jian Zhang[1]

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[1]Shanghai University of Sport, [2]Krembil Brain Institute

Objective: To test and compare the interactions between the ipsilateral dorsal lateral prefrontal cortex (DLPFC) and the motor cortex (M1) of both hemispheres. Methods: Fourteen right-handed subjects participated in the paired-pulse stimulation experiment. In the control condition, the intensity of test stimulus (TS) was adjusted to evoke a motor-evoked potential (MEP) of 1 mV peak to peak in the relaxed first dorsal interosseous (FDI) muscle. In the paired-pulse condition, the conditioning stimulus was set at 110% resting motor threshold (RMT) at 5 cm anterior to the FDI hotspot. Interstimulus intervals (ISIs) between CS and TS were 2, 4, 6, 8, 10, 15, 20, 25 and 30 ms. Results: The two factor ANOVA showed significant interaction between hemisphere and ISI ($F=2.007$, $p<0.05$). Post-hoc analysis revealed significant difference between hemispheres. There was inhibition when CS was applied 2 ms ($p<0.05$) before TS in the right hemisphere but not in the left hemisphere. There was facilitation at 10($p<0.01$), 15($p<0.05$) and 20 ($p<0.05$) ms ISI in the left hemisphere and inhibition in the right hemisphere. In the right hemisphere, an inhibitory effect was found at 10 ms compared to the control condition. Conclusions: The data suggests that the left DLPFC has a facilitatory influence on motor cortical excitability while the right DLPFC has an inhibitory effect. These effects could be mediated by the superior longitudinal fasciculus between the ipsilateral DLPFC and M1. The hemispheric differences may reflect the different cognitive roles the right and left DLPFC may play in movement.

2-F-198 *Opposing effects of cortisol on learning and memory in children using spatial versus response-dependent navigation strategies*

Caroll-Ann Blanchette[1], Vanessa Kurdi[2], Celine Fouquet[2], Russell Schachar[3], Michel Boivin[4], Paul Hastings[5], Philippe Robaey[6], Greg West[7], Veronique Bohbot[2]

[1]University of Montreal, [2]McGill University, [3]University of Toronto, [4]Université Laval, [5]University of California Davis, [6]Ste-Justine research center, [7]Université de Montréal

It is well established that humans use a particular strategy for navigation depending on if they are spatial or response learners. Spatial learners, who display more grey matter in the hippocampus, navigate by building a cognitive map by using environmental landmarks. In contrast, response learners, who show more grey matter in the caudate nucleus of the striatum, navigate by memorizing a series of rigid turns. Previous studies have shown healthy young adults who spontaneously use response strategies (RS) on a virtual navigation task tend to have significantly lower basal levels of cortisol compared to adults who use spatial strategies (SS). Hence, the purpose of this study was to test if these findings would demonstrate a similar pattern among children. Participants were children who attended a laboratory for the study. Cortisol levels were assessed prior to the task, which was the 4 on 8 virtual maze that determines an individual's adopted navigation strategy. Results show that basal cortisol levels have a differential impact on learning and memory between children using navigation strategy (RS vs. SS). Specifically, cortisol

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was found to be beneficial for learning performance among children who used SS. In contrast, cortisol had a deleterious effect on learning the virtual maze task in children who used RS. These findings suggest that individual differences on navigation strategy could help explain differentiating results on how cortisol effects learning and memory.

2-F-199 *The role of for in Drosophila melanogaster social interaction networks (SINs)*

Nawar Alwash[1], Marla Sokolowski[1], Joel Levine[1]

[1]University of Toronto

Drosophila melanogasterdisplay social behaviors such as courtship, mating and foraging in groups. Recent studies have shown that different strains of D. melanogaster also form social interaction networks (SINs) with different properties, suggesting that genes likely influence network phenotypes. The foraging gene (for) encodes a cGMP dependent kinase known to regulate food-related behaviors in many species including the fruit fly D. melanogaster. There are two naturally occurring alleles of the for gene: rover and sitter, where the rover flies are characterized with higher mobility in the presence of food. The finding that for modulates strategies for finding food suggests that it might also contribute to patterns of interaction among flies. However, the role of for in the formation of social networks is unknown. We hypothesize that the for gene influences the formation of SINs and predict that manipulating the for gene would lead to the formation of networks with different SIN properties. Indeed, SINs formed by rover have significantly different properties than those formed by sitter. Our genetic analysis revealed that for copy number affects SIN properties; increasing for copy number was associated with an increase in global efficiency and decrease in assortativity, betweenness centrality and clustering coefficient values. for's conserved role as a modifier of behavior in multiple species including humans suggests that understanding the role of for in the formation of SINs in D. melanogaster will provide insights into how it functions in SIN formation in other organisms.

2-F-200 *Where you look on a face matters! The N170 ERP component is modulated by featural fixation in adults with and without autism spectrum disorder*

Karisa Parkington[1], Roxane Itier[1]

[1]University of Waterloo

A neural eye sensitivity has been reported in neurotypical (NT) adults such that the N170 event-related potential (ERP) elicits a consistently larger amplitude when fixation is enforced on the left or right eye of a face compared to fixation on other parts of a face. ERP studies in adults with ASD report reduced N170 amplitudes or delayed latencies for faces or eyes compared to NT adults;

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however, ERP reports in ASD are inconsistent and have not controlled for visual attention. Here, high-functioning adults with ASD and NT adults viewed faces with fixation enforced on the left eye, right eye, nasion, nose, or mouth during an oddball detection task. Eye movements and electroencephalography recordings were synchronized offline and time-locked to face onset. Preliminary results (ASD = 13;NT = 10) revealed a robust effect of featural fixation. N170 amplitudes were significantly larger when fixation was enforced on the left or right eye compared to all other features and this pattern was consistent across groups. Fixation on the nasion or nose yielded the fastest N170 response in both groups, followed by the left and right eyes, followed in turn by the mouth. No group effects or interactions were found. These findings suggest the neural response to features within a face may be similar for adults with and without ASD when fixation is enforced. Thus, difficulties with eye contact and social communicative behaviours in ASD may not stem from differences in the earliest stages of face perception but may instead be based in free-viewing preferences or later stages of face processing.

2-F-201 *Exendin-4 dose dependently attenuates responding to reward predictive cues in rats*

Ajay Baindur[1], Ken Wakabayashi[2], Karie Chen[2], Malte Feja[3], Kimberly Bernosky-Smith[4], Caroline Bass[1]

[1]SUNY at Buffalo, [2]University at Buffalo, [3]University of Veterinary Medicine Hannover, [4]D'Youville College

Exendin-4 (EX4) is a GLP-1 receptor (GLP-1R) agonist used to control blood sugar levels in type-2 diabetes. EX4 induces weight loss, which is attributed to both its peripheral and central affects, notably in mesolimbic dopamine pathways that mediate cue-induced reward seeking. Behaviorally, GLP-1R agonists influence palatable food preference (e.g. sweet/fat) as well as the motivation to obtain different types of food. Recent data suggests that GLP-1R activity can attenuate cue-induced reward seeking behaviors. In the present study, we tested EX4 (0.6, 1.2, and 2.4 µg/kg i.p.) in an operant model of incentive cue responding, in which the rats must respond to an intermittent audiovisual cue (IC) by nosepoking into nosepoke port to obtain a sucrose reward that is delivered to a reward cup. Metrics centered on the motivational properties of the IC include response ratio (# of rewards earned/# of ICs) and nosepoke latency, while metrics focused on the sucrose reward include total reward cup entries and reward cup entry latency. We found that EX4 dose-dependently attenuates responding to reward predictive cues and increases both the latencies to respond to these cues and to enter the reward cup to consume the reward. EX4 also dose-dependently decreased the number of nosepokes compared to the number of cues presented, however the number of reward cup entries per reward earned was not attenuated. Our findings suggest that EX4 agonism, and by extension GLP-1 signaling can directly modulate the incentive properties of cues attributed with motivational significance.

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2-F-202 *Executive functioning and risk-taking are predicted by the spontaneous navigation strategy*

Etienne Aumont[1], Veronique Bohbot[2], Gregory West[3]

[1]Université du Québec à Montréal, [2]McGill University, [3]Université de Montréal

For one to navigate in an environment, two strategies can be used. The hippocampus-based spatial strategy consists in using multiple landmarks to create a mental map of the environment while the caudate nucleus-based response strategy requires the memorization of a series of directions. A virtual maze assessing one's spontaneous strategy allows the distinction of two groups. Response strategy was previously linked to reduced general cognitive health in older adults. The link with higher cognitive function, however, remained unknown. The present study aimed to explore the links between risk-taking and executive functions (EF) with the spontaneous navigation strategy. Fifty young adults passed through a virtual maze, the Iowa Gambling Task (IGT) and various EF tasks. Results show that spatial learners tend to have reduced risk-taking behaviors by choosing a lower amount of high-risk decks in the IGT. The observed differences might be linked to response learners' more excitable caudate nucleus and its role in the reward circuit. Response learners had enhanced performance on EF tasks they completed more sets and committed fewer perseverative errors in the Wisconsin Card Sorting Test - 64, had longer digit span and had lower flanker reaction time and accuracy cost in an Eriksen flankers task. This supports previous findings linking the caudate nucleus and the striatum to cognitive flexibility, working memory and cognitive control through the frontostriatal loop. This study hints that a navigation training may have interest for improving cognitive functions.

2-F-203 *Regulation of valence learning and discrimination in mice*

T Chase Clark[1], Rosemary Bagot[1]

[1]McGill University

The ability to learn about cues that predict positive and negative outcomes is a basic function necessary for survival. Such associations must be specific but potentially also flexible to allow for updating if their meaning changes. Learning can be influenced by an animal's arousal state, where general arousal can facilitate learning, while high levels caused by stress can impair learning. Here we sought to investigate the interplay between stress, arousal, and learning by training mice on a Pavlovian valence discrimination task. Mice learned to associate a reward (chocolate pellet) with the presentation of an auditory cue (CSR+) and an aversive outcome (footshock) with a distinct auditory cue (CSS+). Appetitive and aversive conditioned responding (head entries to the food port and freezing, respectively) were elevated during their associated CS after training, but not

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during an unpaired CS-. The order in which training was conducted (appetitive or aversive first) influenced acquisition of the appetitive contingency. However, this effect was not seen when cue-valence contingencies were reversed. These results imply that appetitive conditioning interacts with co-occurring aversive conditioning, potentially by impacting the animal's arousal state. Since arousal effects on learning commonly follow an "inverted U", we expect that increasing arousal levels through chronic stress may differently impact learning acquisition.

2-F-204 *Attentional filtering within versus across hemifields in the lateral prefrontal cortex*

maryam nouri kadijani[1], Theda Backen[2], Julio Martinez-Trujillo[3], Jörn Diedrichsen[4], Stefan Treue[5]

[1]Robarts Research Institute, University of Western Ontario, [2]McGill University, [3]University of Western Ontario, [4]Western University, [5]Leibniz-Institut fur Primatenforschung

Attention allows us to focus on only important sensory stimuli in a world full of distractors. However, the ability to allocate attention to important targets becomes more difficult when the distractors are located within the same visual hemifield as compared to when they are in the opposite hemifield. The neural mechanisms underlying this effect remains unclear. We recorded neuronal activity in the lateral prefrontal cortex (LPFC), of two macaque monkeys while they performed a covert spatial attention task with two different conditions. Two stimuli were distributed in either the left and right visual hemifield (across condition) or both within the same visual hemifield (within condition). Here, we show that behavioral performance in non-human primates was lower in the within condition than in the across condition. Moreover, the proportion of single neurons in the LPFC, showing selectivity for the attended location was significantly reduced in the within relative to the across condition. Additionally, we demonstrate that the activity of single neurons and simultaneous neuronal ensembles in LPFC can accurately decode attentional signals in across condition rather than within condition. Ensemble decoding accuracy was sensitive to the noise correlation structure and dynamics of the neural ensembles. Noise correlation also plays various roles in across condition than within condition task. This finding places evidence for independence capacity to attentional selection in the left and right visual hemifields.

2-F-205 *Serotonin mediates C. elegans associative learning by indicating the presence of food*

Safa Ansar[1], Sara Campitelli[1], Daniel Merritt[1], Derek van der Kooy[1]

[1]University of Toronto

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The nematode worm Caenorhabditis elegans, despite having only 302 neurons, has the ability to learn by way of classical conditioning. Worms exposed to an attractive odorant (such as benzaldehyde) during a period of starvation learn to avoid this stimulus. We hypothesized that this association of stimuli is mediated by serotonergic signalling, which is thought to signal the presence of food in the C. elegans nervous system. When given exogenously, serotonin blocks the benzaldehyde-starvation association, and may therefore negatively regulate the formation of the starvation-odourant associative memory by acting as an appetitive food signal. We find that worms mutant for all of the five canonical serotonin receptors (ser-1, ser-4. ser-5, ser-7, mod-1) are able to form a starvation-odourant memory even in the presence of exogenous serotonin. Analysis of single-receptor mutants revealed that ser-4 is the sole receptor necessary for mediating the serotonin/food signal. We are studying the molecular mechanisms underlying this neural pathway to delineate a full circuit diagram, linking the initial perception of food to its ability to block food/starvation learning.

2-F-206 *Locus coeruleus activity in a classical conditioning task*

Mohsen Omrani[1], Mina Ghbrial[1], Janusz Rajkowski[1], Gary Aston-Jones[1]

[1]Rutgers University

Locus coeruleus (LC) is a small brainstem nucleus and is the nearly exclusive source of norepinephrine (NE) to neocortex. Many previous studies have proposed a role for LC in learning. To further explore this idea, we recorded unit activity in waking rats during a classical conditioning paradigm. During the paradigm, in each block the rats received a tone alone (neutral stimuli (NS) in an unconditioned block) or a similar tone followed by air puff to the face (conditioned stimuli (CS) in a conditioned block), while the rat was hanging in a sling. LC neurons exhibit two modes of firing activity: phasic and tonic. In a sensory driven decision task, sensory stimuli that are relevant to the task (targets) evoke phasic responses in LC as opposed to similar stimuli with no task relevance (distractors). Both NS and CS tones evoked phasic LC activity in our paradigm. We were interested to know whether phasic LC responses differ for similar tones in different contexts. The NS does not have a predictive value, but through conditioning the animal learns that the CS predicts the occurrence of the aversive air puff. Therefore, we initially expected an enhanced phasic response to the CS tone as opposed to the NS tone. To our surprise, phasic responses were smaller in the conditioned block (i.e., for CSs) as compared to the unconditioned block (i.e., for NSs). On the other hand, tonic LC activity (the activity in between tones) was significantly larger in the conditioned blocks, consistent with a role for increased NE release in learning the CS-US association.

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2-F-207 *K-means feature detection within sleep and wake brain states: A study with local field potential recordings in a freely behaving rat*

Pauline Balogun[1], Karim Ali[1], Masami Tatsuno[1]

[1]Lethbridge University

The hippocampal activity is often used to define sleep and wake brain states and serves as an indicator of the global brain state. However, recent findings in an fMRI study revealed mismatches between the global sleep state registered in the hippocampus and association cortices and a local state in primary cortical regions. We investigated whether one such region, the primary motor cortex (M1), displays similar local desynchronization during sleep and wakefulness in rats. Local field potential recordings were obtained simultaneously from M1 and the hippocampus of seven, male Fischer-Brown Norway rats. Following spectral analysis, principal component analysis was used to reduce the dimensionality of the datasets, which were then divided into 0.5 second bins. An unsupervised learning algorithm, k-means, was then applied, clustering the bins together according to underlying features. Each bin was assigned a gross behavioural category to create behavioural identities for the clusters. We found there were significantly more cortical clusters than hippocampal ones, suggesting a cortical-hippocampal separation. Certain clusters contained features contrary to the hippocampal brain state such as K-complexes during hippocampal REM sleep. We also found a movement gradation in the detected clusters that was conserved within and between subjects. The results suggest that local desynchronization does occur in the rat M1 and could have repercussions for our understanding of hippocampal-cortical interaction during sleep.

2-F-208 *Lateral entorhinal cortex selectively routes mnemonic features of stimuli to the medial prefrontal cortex*

Xiao Yu[1], Justin Jarovi[1], Kaori Takehara-Nishiuchi[2]

[1]University of Toronto St. George, [2]University of Toronto

The ability to link events across time is a key aspect of everyday memory and depends on inter-connected regions in the forebrain. Among them, the prefrontal cortex and the rhinal cortex are presumed to work in concert by exchanging information because their oscillatory activity becomes synchronized during the retrieval of temporal aspects of event associations in humans (Watrous et al., 2013) and rats (Takehara-Nishiuchi et al., 2011). However, the exact type of information transferred remains unknown. Here, we pharmacologically inactivated the lateral entorhinal cortex (LEC) and examined its impact on oscillatory activity in the medial prefrontal cortex (mPFC) while rats associated one of two neutral stimuli with a mildly aversive eyelid shock. LEC inactivation impaired the encoding of the stimulus-shock association. In parallel, with learning, beta and gamma band activity in the mPFC came to ramp up toward the expected shock onset while the

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phasic increase of wideband power during the stimulus was weakened. LEC inactivation abolished both types of learning-related changes without affecting the oscillatory activity in response to the other neutral stimulus presented alone. Thus, the integrity of the LEC is necessary for the development of mPFC oscillatory activity signaling the temporal stimulus association but not for stimulus-evoked activity in general. This counters the traditional view positing the LEC as a passive relay of stimulus information while supporting an emerging view that the LEC provides other regions with highly integrated information about experiences.

2-F-209 *Computational evidence for a novel role of neurogenesis in memory generalization*

Lina Tran[1], Sheena Josselyn[2], Blake Richards[2], Paul Frankland[2]

[1]The Hospital for Sick Children, [2]University of Toronto

The dentate gyrus of the hippocampus is one of two niches in the adult mammalian, where newborn neurons are constantly integrated into the local circuitry throughout life. The importance of the hippocampus in learning and memory is well characterized, however, the effects of adult hippocampal neurogenesis on cognition are still unclear. Hippocampal neurogenesis has been implicated in pattern separation, cognitive flexibility, temporal integration, forgetting and mood regulation. Here, we propose a novel role of neurogenesis in memory generalization, that is, the ability to extract statistical regularities from previously encountered data in order to adapt performance on new, previously unseen data. Immature neurons (3-4 weeks of age) in the dentate gyrus are hyperexcitable, have fewer inhibitory inputs, and are more plastic than their mature counterparts. We predict that this combination of unique physiological properties of immature neurons in the dentate gyrus, a region known for its sparse firing, may contribute noise to neural activity during learning. It is well known in machine learning that noise injection is one way to prevent overfitting in artificial neural networks (ANNs). By implementing neurogenesis in different ANN architectures, we can test the hypothesis that neurogenesis is one such mechanism of noise injection that the brain employs for the purpose of generalization. Preliminary data suggest that neurogenesis enhances generalization in the MNIST handwritten digits and CIFAR10 image classification task as well as accelerate training.

2-F-210 *Neurogenesis impairs fear expression and alters CA1 population dynamics during memory recall*

Adam Ramsaran[1], Andrew Mocle[1], Lina Tran[2], Alexander Jacob[1], Jessica Jiménez[3], Mazen Kheirbek[4], Sheena Josselyn[1], Paul Frankland[1]

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[1]University of Toronto, [2]The Hospital for Sick Children, [3]Columbia University, [4]UCSF

Our lab has shown in silico (using an ANN) and in vivo (using interventions like voluntary running in mice) that high rates of neurogenesis following memory formation causes forgetting of hippocampus-dependent memories. What remains poorly understood is how the integration of newly-generated neurons into DG-CA3 circuits impairs the retrieval of memory representations in downstream brain regions. To address this question, we used custom miniature endoscopes to monitor the activity from thousands of CA1 neurons while mice formed a contextual fear memory and recalled this memory during two test sessions. Memory was intact in all mice during the recent test, after which we provided running wheels to a subset of mice for one month to promote neurogenesis. During the remote test, mice that ran showed robust forgetting compared to controls. We analyzed single-cell data from each session and observed that neurogenesis did not alter the number of neurons activated during each session. Using machine learning classifiers, we further found that behavioral states (freezing versus non-freezing) could be reliably decoded from neuronal activity in all mice during the recent test. However, freezing classification was diminished in mice with elevated neurogenesis during the remote test, suggesting that CA1 population dynamics poorly represent memory-related states following forgetting. These preliminary results reveal the functional consequence of hippocampal neurogenesis on CA1 population activity and begin to address the neural circuit mechanism by which forgetting occurs in the brain.

2-F-211 *Hierarchically-organized attentional sets bias both information-sampling and choices to feature values, feature dimensions, and contextual information during rule-based learning*

Marcus Watson[1], Benjamin Voloh[2], Milad Naghizadeh[3], Thilo Womelsdorf[2]

[1]York University, [2]Vanderbilt University, [3]University of Lethbridge

In goal-directed tasks both gaze and choice are guided by flexible representations of task relevance that are not fully understood. To better understand their structure and development, we tracked gaze in a complex learning task where putative differences between gaze and action were maximized. Participants performed a context-dependent feature-based object selection task in a complex three-dimensional environment, in which they used a joystick to choose between two objects with multiple feature dimensions. Trial contexts determined which feature values were rewarded. Reward-rule learning occurred in a step-like fashion at "learning points" (LPs), with choice accuracy at or below chance beforehand and near perfect afterward. Simultaneously, selection times dropped, and targets were preferentially fixated. Four distinct findings showed the impact of attentional sets. First, participants were more likely to reach an LP after having previously selected objects with non-rewarded features on relevant dimensions. Second, LPs were reached more quickly when relevant dimensions had also been relevant in the previous block. Third, performance was worse and fixational biases to the target were weaker when

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contexts varied between trials. Finally, after learning one context rule, performance in the other context was better for objects that were rewarded in both contexts. These findings demonstrate the costs of switching attention between, rather than within, dimensions, across multiple time scales and various stages of learning. They point to the existence of hierarchical representations that organize expected values of features, feature dimensions and contexts, in largely the same way for both information sampling and choice.

2-F-212 *To exclude or not to exclude: systematic bias introduced by quality control in pediatric imaging research*

Hajer Nakua[1], Natalie Forde[2], Colin Hawco[2], Aristotle Voineskos[2], Anne Wheeler[3], Meng-Chuan Lai[2], Peter Stazmari[2], Russell Schachar[3], Evdokia Anagnostou[3], Paul Arnold[4], Jason Lerch[3], Stephanie Ameis[2]

[1]University of Toronto, [2]Centre of Addiction and Mental Health, [3]Sick Kids Hospital, [4]Hotchkiss Brain Institute

Background: Behavioural problems in children are associated with scan artefacts in Magnetic Resonance Imaging (MRI) which may lead to bias in brain imaging research results. These artefacts are more prominent in clinical samples. Here, we examined whether different quality control (QC) procedures for structural MRI resulted in exclusion of children with more clinical impairment in a large neurodevelopmental neuroimaging sample. Methods: T1-MRI, behavioural and clinical measures from children in the Province of Ontario Neurodevelopmental Disorders (POND) network (n = 467) were used. Participant exclusion based on motion related artefacts or poor scan quality were carried out using a step-wise QC protocol. T-tests were used to compare mean age, psychopathology, and everyday/adaptive functioning for included versus excluded groups. Results: Three QC approaches were examined: exclusion by visual QC only (n=67), visual and automated QC (lenient group, n=85; stringent group n=100), and automated QC only (MRIQC Random Forest Classifier; n=59). All methods showed a bias towards excluding the youngest participants ($p<0.001$) and those with lower adaptive functioning ($p<0.05$). With increasing stringency, there were greater impairments in adaptive functioning and increased psychopathology for excluded versus included groups ($p<0.05$). The automated QC approach resulted in significant differences in impairment of adaptive functioning and psychopathology despite having excluded the least number of participants. Conclusions: Our preliminary findings suggest that the QC approach chosen may bias analysed samples toward exclusion of younger and more impaired participants. Our next step will be to examine the extent to which brain-behaviour relationships differ depending on the QC method.

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G - Novel methods and technology development

2-G-213 *Triggering naturalistic and synthetic sequences of optogenetic stimulation with an Arduino-based pattern generator*

Hendrik Steenland[1], Lyla El-Fayomi[2], Michael Bergamini[2], Derek van der Kooy[2]

[1]NeuroTek, [2]University of Toronto

Optogenetics can manipulate neural activity, and consequently behavior, in a temporally precise way (Boyden et al., 2015, Nat. Neuro.). The majority of this work has focused on synthetically generated tonic or phasic laser light patterns (e.g. Chaundhury et al., 2013, Nature); however, natural spike trains have much more variation as a consequence of biology when compared to these synthetic patterns. The current engineering project describes an open source, cost effective, Arduino-based method to trigger optogenetic stimulation based on neuronal spike sequences. Neuronal (naturalistic) spike data was collected from putative dopaminergic, glutamatergic and GABAergic neurons in the ventral tegmental area of freely-behaving mice using electrophysiology. Spikes were sorted off-line, and converted to a series of 3msec wide 5 Volt pulses and stored as *.wav files. Synthetic, tonic pulses were also generated and equated for average frequency with the naturalistic data. A printed-circuit board was designed to retrieve these files from a SD card via interaction with the Arduino. Triggering the onset of one of two *.wav files occurred when the mouse broke an infrared beam. The infrared sensing system was encapsulated in a low-cost, 3D printed insert and secured to a commercial, conditioned-place preference testing chamber. The Arduino logs both the time of day and the timing of behavioral events during each experiment. On-going experiments are examining the utility of naturalistic optogenetic stimulation of the ventral tegmental area in comparison to synthetic patterns.

2-G-214 *Optogenetically eliciting precisely-timed action potentials in cerebellar Purkinje cell axons*

Kim Gruver[1], Alanna Watt[1]

[1]McGill University

Optogenetics is a state-of-the-art tool for interrogating neural circuits. In the cerebellum, Purkinje cells serve as the sole output of the cerebellar cortex where they synapse on neurons in the deep cerebellar nuclei (DCN). To investigate the properties of this synaptic connection, we sought to elicit time-locked single action potentials in Purkinje cells. We used transgenic mice expressing channelrhodopsin-2 (ChR2) under the pcp2 promoter targeting Purkinje cells and optically activated ChR2 with a patterned spatial illuminator and blue light from an LED (470 nm). To optimize axonal ChR2-stimulation, we used whole-cell patch clamp recordings of ChR2-expressing Purkinje cells from acute cerebellar slices to determine the conditions that were

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necessary for robustly and reliably eliciting single action potentials. We compared ChR2-stimulation in axons and cell bodies from individual Purkinje cells and found that a longer light pulse was necessary to elicit single action potentials from axons. To explore axonal ChR2-stimulation conditions further, we exposed cells to ambient light prior to optogenetic activation and found that this caused both cell bodies and axons to be less sensitive to focused optogenetic activation. However, axons were nearly two-fold more affected than cell bodies. Finally, using our empirically-determined optimal axonal ChR2-stimulation, we elicited time-locked IPSCs in DCN neurons with minimal jitter. This allows us to optogenetically explore Purkinje cell connectivity in the cerebellum.

2-G-215 *A knock-in strategy to study protein localization in human induced pluripotent stem cell (iPSC)-derived cortical neuron through genome editing*

Quanwei Lyu[1], Ruolin Fan[1], Yat-Ping Tsui[1], Ying-Shing Chan[1], Daisy K.Y. Shum[1], Kwok-On Lai[1]

[1]The University of Hong Kong

The emergence of human induced pluripotent stem cells (hiPSCs) and their ability to differentiate into multiple subtypes of neuron present the attractive potential as a cellular model to study human-specific neural properties. Furthermore, the graft of hiPSC-derived neurons into the mouse brains potentially allows exploration of how synaptic connections form in vivo. To distinguish the synaptic proteins of the grafted neurons from those of the host neurons, it is desirable to specifically label the proteins of interest in hiPSC-derived neurons. Here in this proof-of-concept investigation, we use CRISPR-Cas9 to create a knock-in epitope tag to study the localization of endogenous beta-actin in hiPSC-derived neurons. We have developed the differentiation protocol for the IMR90-hiPSC cell line to generate mature cortical neurons that express excitatory synaptic makers and produce miniature excitatory postsynaptic current. Through CRISPR-Cas9 mediated genome editing, the beta-actin gene was edited in hiPSC such that a hemagglutinin (HA) tag was added to the N-terminal of beta-actin. After differentiation of the edited hiPSCs into cortical neurons, the growth cones and dendritic spines were visualized by immunostaining through anti-HA antibody. The hiPSC-derived neural stem cells were also grafted into the mouse brain to visualize the grafted human neural stem cells by anti-HA immunoreactivity in vivo. Our findings suggest the feasibility of this strategy to label synaptic proteins for the study of protein localization during synaptogenesis in human iPSC-derived cortical neurons

2-G-216 *3D modeling of cerebral sinuses to detect abnormal venous drainage in mild traumatic brain injury: 9.4T MRI animal studies*

Qandeel Shafqat[1], A. Max Hamilton[1], Jennaya Christensen[1], Elizabeth Imhof[1], Richelle Mychasiuk[2], Jeff Dunn[1]

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[1]University of Calgary, [2]Monash University

Recent studies suggest cerebrovascular changes are implicated in mTBI. To better understand this aspect of mTBI, we conducted two studies utilizing 9.4T MRI to assess sinus size as a marker of abnormal venous drainage. We hypothesized that changes in drainage after mTBI will be indicated by differences in sinus size. Using two well-developed mTBI animal models, we analyzed 3 cerebral sinuses that regulate venous drainage; the superior sagittal sinus (SSS) and left and right transverse sinuses. In both studies, rats were divided into sham or mTBI groups and underwent brain MRI 1 day or 2-wks post-mTBI. In study 1, we used a weight-drop model to induce mTBI and utilized RARE anatomical imaging. Since the weight-drop model injures the top of the head where the SSS lies, study 2 employed a lateral impact model to prevent direct injury. In addition, animals underwent gadolinium enhanced imaging which improved visualization of the sinus lumen. The MRIs were turned into 3D models in 3D Slicer. This provided sham and mTBI sinus volumes for comparison. Results show the mTBI groups experience an acute increase in sinus size that recovers to normal 2-wks post mTBI. Our research is novel in that we use MRI, an imaging modality generally not sensitive to acute changes in mTBI to show a distention in sinus size. Sinus dilation may be a response to abnormal venous regulation post-mTBI and our MRI methods are effective in detecting this. Our findings support the hypothesis of abnormal vascular regulation and provide evidence that dilation of draining sinuses may be a marker of injury.

2-G-217 *Controlling robot PLEN.D by EEG on recalling ten images of its movement*

Takahiro Yamanoi[1], Hiroshi Takayanagi[2], Hisashi Toyoshima[3], Toshimasa Yamazaki[4], Michio Sugeno[5]

[1]Hokkai-Gakuen University, [2]Fudan University, [3]Japan Technical Software, [4]Kyushu Institute of Technology, [5]Tokyo Institute of Technology

The paper is concerned with brain machine interface to control a robot. We measured electroencephalograms (EEGs) when three subjects were recognizing and, then, recalling, i.e., imaging the ten movements of a robot PLEN.D displayed on a PC monitor. Of the 19 channels, we analyzed data from channels Fp2 (No. 2), F4 (No. 4), C4 (No. 6), and F8 (No. 12) according to the International 10-20 system, since these points of channels lie above the right frontal area. Although EEGs are time series data, we regarded them as vector-valued in the 84 dimensional space (4 channels x 21 time-points). Then we sampled EEGs from 400ms to 900ms at 25ms intervals. We call it the data1. We also sampled the data from 399ms to 899ms (data 2) and from 398ms to 898ms (data 3). Each set of samples yields 21data points from each channel for each sampling period. By these three sets of data, the number of sampling EEG data are tripled, we call these the tripled data. The obtained data are considered as 84 dimensional vectors. The number of external criteria is 10: the number of different robot movements and that of explanatory variables is 84: EEG data. The canonical discriminant analysis was applied to the tripled sampled

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single-trial-EEGs. The results were obtained by applying the jack knife algorithm, where discrimination ratio was found to be 100% for each subjects. Then, the discriminant results were transmitted to the robot PLEN by way of Bluetooth. We found that the robot was successfully controlled with the ten commands obtained by single-trial-EEGs taken from the subjects.

2-G-218 *Using kinematic and qualitative analyses in a rat model of stroke to quantify recovery after repetitive transcranial magnetic stimulation*

Zanna Vanterpool[1], Julia Boonzaier[2], Michel Bernabei[3], Huub Maas[1], Rick Dijkhuizen[2]

[1]Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, [2]University Medical Center Utrecht and Utrecht University, [3]Northwestern University

Animal models are used to elucidate the effects of novel therapeutic brain stimulation techniques on sensorimotor recovery following stroke. Unfortunately, conventional preclinical behavioral outcome measures are limited in distinguishing between true recovery and compensation. The aim of this study was to quantify functional motor recovery of the impaired forelimb after repetitive transcranial magnetic stimulation treatment (rTMS), using (novel) kinematic and (standard) qualitative assessments. Nine male Sprague-Dawley rats were trained in the single pellet reaching task and received a photothrombotic stroke in the motor cortex. Rehabilitative therapy consisted of environmental enrichment and rTMS treatment involving either sham stimulation, high frequency (5 Hz, ipsilesional), or low frequency (1 Hz, contralesional) stimulation of the motor cortex. Motor recovery was assessed at day 3, 16, and 23 after stroke, through frame by frame video analysis of pellet reaching. In all experimental groups, we observed recovery following initial impairments, reflected by changes in movement duration, peak velocity, and smoothness. Qualitative assessment of pellet reaching suggested a performance-enhancing effect of high frequency rTMS, which was however not detected in the kinematic analysis. Despite the ambiguous effects of rTMS on functional recovery, our findings reflect the potential of kinematic analysis for detailed assessment of (changes in) motor impairments in rodents. This method may ultimately contribute to a better alignment of preclinical and clinical research.

2-G-219 *Cross-frequency coupling features in scalp and intracranial EEG identify postictal generalized EEG suppression state*

Vasily Grigorovsky[1], Berj Bardakjian[1]

[1]University of Toronto

In patients with epilepsy, seizures are often followed by postictal generalized EEG suppression (PGES) - a state characterized by reduced background activity. Several studies previously

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suggested that PGES is the result of total cessation of neuronal activity. However, recent work from our lab highlighted the presence of unique low-to-high frequency coupling during PGES that not only suggested that there are underlying dynamics during this seemingly quiescent state, but also could be used for identification of PGES from other non-ictal states. Since that work was done in intracranial EEG (iEEG) for higher data fidelity, we hypothesized that similar cross-frequency coupling features can be found using scalp EEG data. To test that assertion, we used EEG-iEEG paired recordings from three patients with Engel Class 1 surgical outcome. In each case we identified the PGES and an artifact-free preictal state of the same window size. Using index of cross-frequency coupling (ICFC) we identified the degree of coupling and dominant frequency bands involved in both the iEEG version of PGES (used as the control) and the scalp EEG PGES trace. Furthermore, we quantified areas of high ICFC in both cases. We found that despite potential signal attenuation due to bone conduction and artifacts in scalp EEG, we were able to capture an increase in ICFC in EEG trace of PGES and identify coupling between frequency bands similar to those seen in iEEG (0.5-1 Hz coupled with 30-40 Hz). This result suggested that ICFC features could be successfully used to identify PGES states even in scalp EEG.

2-G-220 *3D bioprinting of starch-chitosan scaffolds for engineering neural tissues*

Haley Butler[1], Andrew Tasker[1], Debra MacDonald[1], Ali Ahmadi[1]

[1]UPEI

A tissue engineering scaffold is a 3D biocompatible, biodegradable and porous structure that is a temporary template for cell and tissue ingrowth. At present, most 3D scaffolds are based on synthetic materials, which have desirable mechanical properties, but often lack biocompatibility. Potato starch and chitosan are natural polymers suitable for 3D scaffold design. Our overall aim is to determine if differing formulations of these polymers can be used successfully for the bioprinting of neurons, glia and vascular endothelial cells in support of in vitro studies of the factors that influence drug disposition and function in the CNS. Immortalized neuronal (Neuro2a) cells were seeded on different previously-characterized formulations of the natural bio-inks and incubated under standard cell culture conditions for varying times. The biocompatibility/cytotoxicity of each formulation was examined by determining a live/dead count compared to appropriate controls using the fluorescent dyes propridium iodide and calcien blue. The neuronal cells were then embedded inside the preferred scaffold material(s) using different formulation techniques and a live/dead ratio was determined using various immunohistochemical markers and confocal microscopy. Results obtained to date indicate that Neuro2a cells show only slightly reduced viability when seeded on to natural polymer formulations applied to 0.4 um porous minicell inserts and cultured for up to 4 days. Further studies to optimize conditions that will support 3D bioprinting of neurons are currently in progress.

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2-G-221 *Establishing the immune profile of cerebrospinal fluid from dogs with central nervous system diseases (preliminary results).*

Tamara Morrill[1], Fiona James[1], Janet Beeler-Marfisi[1], Olaf Berke[1], Stefan Keller[1]

[1]University of Guelph

Central nervous system (CNS) diseases in dogs can be challenging to diagnose due to non-specific clinical findings. Immune profiling characterizes 'immune signatures' by next-generation sequencing (NGS) of lymphocyte antigen receptor (LAR) gene repertoires, which could be used to diagnose CNS diseases using cerebrospinal fluid (CSF). This study's objectives were to 1) determine whether DNA yield reliably predicts that immune repertoires can be sequenced from a given sample 2) characterize immune repertoires in CSF from dogs with CNS diseases. Cerebrospinal fluid was collected from 6 dogs with neurologic disease as a part of routine neurological examination. DNA was extracted from cell-associated (ca) and cell-free (cf) fractions and LAR genes were sequenced using the Illumina Miseq system. Data were analysed using the Interrogate/ARResT bioinformatics platform. The average DNA yield was 1.42 ng/uL (0-7.45 ng/uL) and 0.395 ng/uL (0.11- 0.657 ng/uL) for the ca and cf fractions, respectively. The number of sequencing reads varied between samples. DNA yield correlated weakly with the number of sequencing reads (r= 0.15) indicating DNA yield as a poor predictor of sequencing output. A greater number of sequencing reads were obtained from the ca fraction in 4/6 samples suggesting that the ca fraction is more useful. These preliminary data suggest that LAR genes can be sequenced from a subset of CSF samples in dogs. Future studies will be directed at refining the sequencing protocol and at assessing the utility of CSF cell count and cell differential count as predictor variables.

2-G-222 *Adapting miniscopes technology for in vivo calcium imaging in deep brain structures of freely moving rats*

Thomas Bassett[1], Ken Wakabayashi[1], Caroline Bass[2]

[1]University at Buffalo, [2]SUNY at Buffalo

Calcium imaging permits the correlation of behaviors to individual firing patterns of specific neuronal populations. Calcium imaging relies on genetically encoded calcium indicators (GECIs), which fluoresce with calcium release during neuronal firing. Fluorescent signals can be captured by a surgically implanted GRadient INdex (GRIN) lens, which transports the signals from the targeted neuron to a CMOS camera sensor mounted outside the skull in a head-mounted miniaturized housing (e.g. miniscope). The aim of this project is to adapt miniscope technology, which has been optimized in mice, to imaging deep brain structures in freely behaving rats, specifically the nucleus accumbens. The challenges to rats in these experiments include the greater strength of the rat, which tests the durability of the miniscope design, and increased brain

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size that requires GRIN lengths that are difficult to fabricate. In this project, we report successful recording of NAc GECI images in freely moving rats, and correlated these signals to extracellular glucose measurements, another index of brain activity. We present several possible solutions for adapting this technology to rats, including increasing the durability of the miniscope hardware at key points of failure, optimizing viral transduction, and GRIN fabrication. Further strategies on how we can adapt these miniscopes for reliable imagining of deep brain structures in freely moving rats will be discussed in detail.

2-G-223 *Investigating the effects of dexamethasone on vascular permeability and inflammatory response following focused ultrasound and microbubble-mediated BBB treatment*

Dallan McMahon[1], Wendy Oakden[2], Kullervo Hynynen[1]

[1]University of Toronto, [2]Sunnybrook Research Institute

Introduction: Preclinical research has demonstrated the utility of focused ultrasound (FUS) and microbubbles (MBs) to transiently increase BBB permeability for therapeutic agent delivery; however, recent work has shown that some degree of inflammation accompanies this increase in BBB permeability. Dexamethasone (DEX), a corticosteroid, has anti-inflammatory properties and is known to rapidly reduce BBB permeability in brain tumours. Work presented here explores the effects of post-sonication DEX administration on BBB permeability and inflammation. Methods: Male Sprague Dawley rats received unilateral hippocampal sonication; BBB permeability was assessed 15 minutes later by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI). Following imaging, animals received either DEX (5 mg/kg; intraperitoneal) or saline and were imaged two hours post-FUS+MBs. Protein expression was assessed 2 days post-FUS+MBs Results: Hippocampal Ktrans dropped by 60.8% ± 9.7% and 74.2% ± 10.4% between 15 minutes and two hours following FUS+MBs in saline and DEX, respectively ($p = 0.003$). DEX prevented FUS+MB-induced elevations in the expression of ICAM1, MCP1, VEGF, and GFAP 2 days following sonication. Conclusion: A more rapid return of BBB permeability towards baseline, combined with the anti-inflammatory properties of DEX, may lead to a reduction in the magnitude of the inflammatory response following FUS+MBs. This may provide greater clinical flexibility, allowing repeated treatments in short succession with reduced risk for deleterious effects to accumulate.

2-G-224 *Brain emotional learning-inspired models for long term prediction of EEG*

Mahboobeh Parsapoor[1]

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[1]McGill University

Brain Emotional Learning-inspired Models (BELiMs) is a new category of neuroscience-inspired artificial intelligence (NIAI). BELiMs, which developed by taking inspiration from the neural structure of the fear-conditioning system, have proposed to address time complexity issues associated with NIAI models. BELiMs can address this problem because it is based on the fear-conditioning emotional system that quickly processes fear-induced stimuli to provide emotional responses. Moreover, the development of BELiMs has been motivated by the fact that most NIAI models such as CNN have not shown high performance for long-term prediction of chaotic and dynamic time series. However, BELiMs are based on the neural structure of fear which learns to predict aversive events (that might happen in the far future). Thus, BELiMs are able to predict long-step ahead of chaotic time series. The general structure of BELiMs has been developed based on the connection between different regions of the brain that are responsible for processing emotional stimuli. The function of a BELiM is implemented by assigning adaptive networks to different parts of its structure. The performance of BELiMs as a long-term prediction model has been verified by examining a new variation of BELiMs on Electroencephalogram (EEG) time series (it should be noted that the long-term prediction of time series such s EEG is essential to predict abnormalities in EEG and to develop early detection of mental problems).

2-G-225 *Extracting low-dimensional latent space trajectories from calcium fluorescence signals with deep generative models*

Luke Prince[1], Colleen Gillon[1], Blake Richards[1]

[1]University of Toronto

In-vivo 2-photon calcium imaging permits simultaneous recordings from hundreds of neurons. Such high-dimensional data is ripe for techniques to identify low-dimensional factors driving neural dynamics. However, common methods ignore non-linearity and temporal dynamics in brain activity. To address this, Pandarinath et al. (2018) developed a deep generative model named Latent Factor Analysis via Dynamical Systems (LFADS). However, LFADS was designed for application to spiking data rather than calcium imaging data. We develop two alternatives to LFADS: 1) an extension adding calcium transient generating layers estimating the fluctuating moments of fluorescence signals modelled as shot-noise processes, 2) a generative-adversarial network (GAN) using an alignment kernel discriminator. To examine the performance of our systems, we generated synthetic data from a 50-cell chaotic, recurrent, spiking network by filtering spikes with an exponential kernel and adding white noise. As with the original LFADS, our systems reduced the data to a smaller set of factors and inferred unseen inputs to the network. We assessed performance using the r-squared coefficients between unseen ground-truth firing-rates and activity of rate units in the deep neural network. We show that our LFADS extension performs on par with the original method applied to spike data, and better than a Gaussian process

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approximation, or a deconvolution algorithm to retrieve spikes from fluorescence. We also show that our GAN approach performs better at reconstructing the observed signals than any other approach.

2-G-226 *Development of a diffusion magnetic resonance imaging template for investigating short-ranged U-shaped structural connectivity in the human adult brain*

Jason Kai[1], Ali Khan[2]

[1]Western University, [2]University of Western Ontario

Diffusion magnetic resonance imaging (dMRI) provides a non-invasive method of probing structural connectivity of the brain, providing insight into microstructural properties and inferring attributes of the structural pathways. While anatomical MRI templates (eg. T1-weighted) are available, there are few dMRI templates available which are released as processed diffusion tensor templates. We have developed a population-based, whole-brain dMRI fibre orientation distribution (FOD) template. Data from unrelated, healthy young adult subjects (n=100) scanned on a custom 3-Tesla MRI and released with the Human Connectome Project was used to develop the dMRI template. Data was minimally preprocessed, normalized for image intensity and corrected for susceptibility, eddy current, and subject motion induced distortions. Additional corrections for spatial distortion and blurring caused by gradient non-linearity were performed. Tissue-specific response functions were estimated and averaged for each subject's preprocessed data. Averaged response functions are used to compute the FODs for each subject and intensity normalization is performed on the estimated FODs. The dMRI template is created by first registering the subjects together via the orientation distributions bringing the data into the same space and averaging. The dMRI template enables registration of data to a standard space where further processing may be performed. Applications of the dMRI template include streamline clustering to identify and study unique pathways, such as the short-range U-shaped tracts.

2-G-227 *Functional inference of real neural networks with artifial neural networks*

Mohamed Bahdine[1], Simon Hardy[1], Patrick Desrosiers[1]

[1]Université Laval

Fast extraction of connectomes from whole-brain functional imaging is computationally challenging. Despite the development of new algorithms that efficiently segment the neurons in calcium imaging data, the detection of individual synapses in whole-brain images remains intractable. Instead, connections between neurons are inferred using time series that describe the evolution of neurons' activity. We compare classical methods of functional inference such as

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Granger Causality and Transfer Entropy to deep learning approaches such as Convolutional Neural Networks (CNN) and Long Short-Term Memory (LSTM). Using synthetically generated time series from the C. Elegans connectome, we find that deep learning outperforms classical methods for pair-wise inference. Indeed, using receiver operating characteristic curves, we find that the LSTM always yields a higher true positive rate, that the CNN performs better than Transfer Entropy for small false positive rates, which in turn, performs better that Granger Causality for all false positive rates.

2-G-228 *Hippocampal morphology and cytoarchitecture in the 3D BigBrain*

Jordan DeKraker[1], Jonathan Lau[1], Kayla Ferko[1], Stefan Köhler[1], Ali Khan[1]

[1]University of Western Ontario

The internal architecture of the hippocampus is challenging to map in detail using traditional histology and in-vivo neuroimaging. This is due, in part, to its complex archicortical folding that is difficult to appreciate in both modalities. Here, we aimed to overcome this challenge by leveraging the unique histological dataset available as open-source 3D BigBrain. Specifically, we investigated the relationship between topology, laminar cytoarchitecture, and detailed morphology with respect to hippocampal subfields and its anterior-posterior axis. Inspired by computational parcellation methods used in the neocortex, we topologically 'unfolded' the hippocampus and mapped it with respect to 5 morphological and 10 laminar features. Several features, including thickness, gyrification, and mean neuronal density, clearly differed between subfields. Indeed, data-driven clustering of all features revealed subdivisions which closely resemble manually defined subfields. Some features, most notably gyrification, also showed anterior-posterior differences within subfields, which may relate to connectivity and functional differences described in previous literature. Overall these findings offer quantifiable markers of hippocampal subfields, and provide new anatomical insight into the topology and properties of hippocampal tissue. Future applications could involve translation to in-vivo MRI for probing the internal hippocampal architecture at this mesoscale in cognition and disease.

H - History, teaching, public awareness and societal impacts in neuroscience

2-H-229 *The convergence curriculum: Arts, neuroscience, and society*

Cristian Zaelzer[1], Bettina Forget[1]

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[1]Convergence, Perceptions of Neuroscience / Concordia University Faculty of Fine Arts

"Convergence: Arts, Neuroscience, and Society" is a two-semester interdisciplinary, interuniversity course, where 12 neuroscience students (MSc, PhD, Trainees) from the McGill University Integrated Program in Neuroscience (IPN) and 14 fine art students (BA) from Faculty of Fine Arts (FoFA) from Concordia University work together to create collaborative sci-art projects. The curriculum was developed as part of the Convergence Initiative, a non-profit organization that aims to foster the general public's understanding of neuroscience by fusing art and science. The curriculum offers a challenging and stimulating combination of lectures, debates, site visits, and workshops. Through independent study, collaborative studio work, and group discussions, the students discover territories outside their scientific and artistic comfort zones. The developed pedagogy transcends disciplinary boundaries by focusing on research practice, public outreach, and questioning disciplinary stereotypes. The 2018/2019 iteration of the Convergence course culminated in an art exhibition that featured an integrated science symposium. The students produced 12 collaborative artworks which artistically interpreted contemporary neuroscience research. Concurrent with the art exhibition, a two-day neuroscience symposium allowed the students to present their science communication media projects to the general public with non-traditional methods learned during the length of the course. In this poster, we share the methods and experiences from this year's course.

Poster cluster: Rodent cognitive neuroscience

2-Cluster-230 *In vivo modulation of microglial activity using chemogenetics*

Aja Hogan-Cann[1], Diana Sakae[1], William Binning[1], Matthew Maksoud[2], Valeriy Ostapchenko[2], Mohammed Al-Onaizi[1], Sara Matovic[3], Wataru Inoue[2], Wei-Yang Lu[2], Vania Prado[2], Marco Prado[2]

[1]Robarts Research Institute, University of Western Ontario, [2]University of Western Ontario, [3]Robarts Research Institute

Microglia, the immune cells of the central nervous system, survey their surroundings and respond to external stimuli to maintain homeostasis in the brain. To do this, microglia express an array of receptors that allow them to receive and respond to signals from neighboring cells. Many of these receptors are G protein-coupled receptors, which regulate a variety of microglial functions through different signalling pathways. We have generated mice expressing either Gq (hM3Dq) or Gi (hM4Di) Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) selectively in microglia. These mutated muscarinic receptors no longer respond to their endogenous ligand acetylcholine, but they can be activated by clozapine-N-oxide (CNO) or clozapine, at doses that are inert at other receptors. In both Gq and Gi DREADD mice, the recombinant receptor is expressed selectively in microglia. Activation of microglial Gq or Gi DREADD by CNO initiates Gq and Gi intracellular signalling pathways, respectively. Furthermore, activation of either signalling

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pathway, by intraperitoneal injection of CNO, does not seem to affect baseline behaviour. Remarkably, chronic activation of microglial Gq signalling in mice, by CNO injection, decreased the expression of pro-inflammatory cytokines in the brains of LPS-injected mice. This chemogenetic method of manipulating microglial activity could therefore be applied to diseases where microglia dysregulation leads to neuroinflammation. Acknowledgements: Supported by CGSM, CIHR, Alzheimer's Society of Canada.

2-Cluster-231 *Cholinergic regulation of plaque pathology in an Alzheimer's disease mouse model*

Liliana German-Castelan[1], Takashi Saido[2], Takaomi Saido[2], Marco Prado[3], Vania Prado[3]

[1]Western University, [2]RIKEN Brain Science Institute, [3]University of Western Ontario

Cholinergic deficiency is a characteristic of many neurodegenerative disorders including Alzheimer´s disease (AD), the most common form of dementia. Decreased levels of the vesicular acetylcholine transporter (VAChT) have been detected in early AD patients compared to controls, and previous work suggested that cholinergic deficiency can increase AD-like pathology in mouse models. In humans, plaque pathology has been linked to the loss of VAChT, however, whether changes in VAChT levels have a causal relationship with plaque accumulation is unknown. To study this aspect of AD, we crossed a humanized APP knock-in mouse carrying 3 AD-associated mutations (AppNL-G-F) with mice overexpressing VAChT using a BAC transgene. We analyzed the number and area populated by Aβ plaques in the cortex and hippocampus, as well as VAChT levels at different ages. Our preliminary results show a significant decrease in plaque area in the cortex at 2 months, but not at 3 or 6 months of age. Remarkably, we observed a sharp decrease in the levels of VAChT in AppNL-G-F-VAChT-BAC transgenic mice at 6 months, effectively reducing the overexpression of VAChT. Accordingly, AppNL-G-F mice presented age-decreased VAChT levels at 3 and 6 months when compared to 2-months of age. Moreover, elimination of cortical VAChT increased the number of plaques in AppNL-F mice, a humanized model with less aggressive pathology. These results suggest that cholinergic tone modulates plaque accumulation in a humanized AD mouse model and that plaque accumulation can interfere with cholinergic tone by modulating VAChT levels.

2-Cluster-232 *Prefrontal contributions to metacognitive decision making in the mouse*

Daniel Palmer[1], Sheena Josselyn[2], Timothy Bussey[3], Lisa Saksida[3]

[1]Western University, [2]University of Toronto, [3]University of Western Ontario

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Metacognition is the ability to use internal cognitive state information to adjust and modify behaviours. The ability to adjust behaviour in response to metacognitive evaluations is an important component of normal decision making. It is thought that the metacognitive component of decision making may represent an important dimension of conscious experience and may be impaired in disorders such as Schizophrenia. While metacognition has been researched and characterized in humans, there remains many outstanding questions regarding metacognitive processing in animals. Animals such as primates have demonstrated behaviours consistent with metacognition. Here, in order to assess metacognition in mouse models, we have developed two new tasks of metacognition using the touchscreen equipped operant chamber system. In the 'prospective' task, mice are given an option to escape difficult trials prior to visual discrimination, while in our 'retrospective' task mice gamble on their previous visual discrimination decisions. In both tasks, mice display behaviour consistent with metacognitive decision making. In order to determine how the prefrontal cortex contributes to metacognitive processing, fibre photometry will be used to characterize the neural activity of the orbitofrontal cortex and prelimbic in the metacognitive tasks. These structures have been previously implicated in prior research on decision making. Subsequent research will attempt to experimentally manipulate orbitofrontal cortex and prelimbic cortex using optogenetics.

2-Cluster-233 *Fiber photometry reveals dopamine reward prediction-error in the nucleus accumbens of mice during a touchscreen pavlovian autoshaping paradigm*

Miguel Skirzewski[1], Amy Reichelt[1], Julie Dumont[1], Fangmiao Sun[2], Yajun Zhang[2], Yulong Li[2], Jane Rylett[1], Vania Prado[1], Lisa Saksida[1], Marco Prado[1], Tim Bussey[1]

[1]University of Western Ontario, [2]Peking University School of Life Sciences, McGovern Institute for Brain Research

Electrophysiological single-unit recordings have shown that putative midbrain dopamine (DA) neurons generate action potentials when the reward is encountered (unconditioned stimulus, US) as well as during a stimulus that predicts a reward (conditioned stimulus, CS). Interestingly, it seems that the firing of midbrain neurons to the reward itself disappears when it is predicted. Here we used state-of the art automated touchscreens to test mice during a Pavlovian approach (Autoshaping) task (Horner et al, 2013), combined with direct measurements of extracellular DA dynamics in the nucleus accumbens (NAc) using a recently developed genetically encoded GPCR-activation based-DA (GRABDA) sensor (Sun et al, 2018) and fiber photometry. We found that a stimulus presentation associated with the delivery of strawberry flavoured liquid reward (CS+) leads to a robust increase in extracellular DA in NAc. Across six consecutive training sessions (1 session/day), we observed an increase in DA dynamics as well as in the number of spontaneous approaches to the CS+ screen. Moreover, a robust phasic DA release was observed during reward delivery (US). DAergic tone was not altered in untrained mice or following the

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presentation of CS-. Our experiments reveal fast changes in DA tone associated with Pavlovian conditioning in freely-behaving mice performing a touchscreen task, demonstrating the feasibility to determine millisecond-scale changes in neurochemicals contributions to cognitive function. This research was supported by BrainsCAN through the Canada First Research Excellence Fund (CFREF).

2-Cluster-234 *Executive dysfunction in an APP knock-in mouse model of Alzheimer's disease revealed using touchscreen technology*

Julie Dumont[1], Chris Fodor[2], Flavio Beraldo[1], Elisha Jindal[2], Ashwin Harimohan[2], Takashi Saido[3], Takaomi Saido[3], R. Jane Rylett[2], Marco A.M. Prado[2], Timothy Bussey[1], Lisa Saksida[1], Vania Prado[1]

[1]University of Western Ontario, [2]Western University, [3]RIKEN Brain Science Institute

Alzheimer's disease pathology is characterized by the accumulation and aggregation of amyloid β peptides in extracellular plaques. How plaque accumulation in relevant brain areas affects cognition is still not fully understood, because most mouse models of Alzheimer's disease suffer from overexpression of APP-derived peptides under the control of exogenous promoters. APP KI mice have been engineered to express mutated humanized APP under the control of the mouse APP promoter and provide a model to follow the accumulation of plaques in relevant brain regions. The AppNL-G-F/NL-G-F mouse line develops plaques as early as two months of age, whereas the APPNL/NL does not develop plaques. Mice containing either AppNL/NL or AppNL-G-F/NL-G-F mutations were tested in automated touchscreen chambers on a panel of cognitive tests including 5-choice serial reaction time, pairwise visual discrimination and reversal as well as a location discrimination task. These mice were also tested on several non-touchscreen tasks, such as the elevated plus maze and novelty food suppression task. Mice of both sexes presented plaque pathology (AppNL-G-F/NL-G-F) and showed abnormal cognitive flexibility, with some evidence that female have larger attention deficits compared with males. These results suggest that although amyloid plaques are found throughout the cortex, AppNL-G-F/NL-G-F mice show selective cognitive deficits. Critically, the APP KI mice may serve as model of cognitive inflexibility resulting from frontal-striatal dysfunction typically observed in later stages of Alzheimer's disease.

2-Cluster-235 *Optimisation of a touchscreen spontaneous object recognition task in mice*

Amy Reichelt[1], Daniel Palmer[2], Subhan Shaikh[2], Lisa Saksida[1], Timothy Bussey[1]

[1]University of Western Ontario, [2]Western University

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Spontaneous objection recognition (SOR) is a highly sensitive assay of recognition memory that can be used in humans and rodents. However, the test is run very differently between species, with rodents typically exploring physical objects and humans responding to computerised images. In this study we sought to optimise and test an automated version of two trial spontaneous object recognition memory in mice using touchscreens to display real-world three-dimensional rotating images as stimuli. During the sample phase, mice were exposed to two identical images. Following a retention interval (5 or 30 minutes), preference for a novel object was measured by the duration of time the mouse spent approaching and touching the new image, in comparison to approaches to the previously viewed image. Systemic administration of the anti-muscarinic compound scopolamine resulted in significant delay-dependent object recognition impairments, akin to those observed in SOR tasks utilising physical objects. This study demonstrates the characterisation and sensitivity of a novel, high throughput recognition memory platform for use with rodent touchscreens.

2-Cluster-236 *Mouse performance on a novel touchscreen continuous performance task is dependent on signaling in the prelimbic cortex*

Tyler Dexter[1], Anita Taksokhan[1], Daniel Palmer[1], Amy Reichelt[2], Lisa Saksida[2], Tim Bussey[2]

[1]Western University, [2]University of Western Ontario

Attention is the cognitive processing that facilitates the ability to target and attend to relevant environmental stimuli, while filtering out irrelevant or distracting stimuli. Control over selective attention is theorized to be dependent on organized neural communication that stems from the medial prefrontal cortex (mPFC). To evaluate selective and sustained attention, mice were trained on the novel touchscreen rodent continuous performance task (rCPT), a task designed to emulate the human CPT. In the rodent version, images are continuously presented on a touchscreen, where mice have been trained to selectively respond to one image type while suppressing responses to all others. Following training on the rCPT, bilateral cannulas were implanted into the prelimbic (PL) region of the mPFC. Immediately prior to cognitive testing, a mixture of GABA A and B agonists were infused into the PL cortex to temporarily inactivate the structure. Inactivating the PL cortex significantly impaired performance on this task, resulting in a reduced ability to discriminate the target from non-target images, as well as a reduction in speed and overall responding. Currently, mice expressing optogenetic receptors are being used to evaluate how parvalbumin interneuron activity within the PL cortex influences attentional performance on the rCPT. As the parvalbumin interneuron population is heavily implicated in generating coordinated neuronal activity and supporting cognition, it is predicted that inhibiting these interneurons and altering synchronous PL activity will impair rCPT performance.

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Poster cluster: Lipid signalling in the developing brain: link to autism

2-Cluster-237 *Neurogenesis in the adult hippocampus and its role in mood*

Katrina Zmavc[1], Cecilia Kramar[2], Timothy Bussey[2], Lisa Saksida[2]

[1]Western University, [2]University of Western Ontario

The variability in the symptom profiles and treatment response of depression has led to an increased interest in molecular, cellular, and circuit mechanisms of many aspects of mood. Evidence suggests that a reduction in adult hippocampal neurogenesis (AHN) is associated with an increase in depression-like behaviour, as antidepressant treatment promotes AHN and reduces depression-like behaviour. Whether this is due to causal effects of AHN on mood is unclear. Many studies in this area have used conventional behavioural tasks, such as fear conditioning, that are stressful and largely differ from those used in humans. Here, we used touchscreen behavioural chambers - which allow for non-aversive and translational tasks - to test the hypothesis that AHN plays a causal role in mood regulation. Mood-related touchscreen tasks used include probabilistic reversal learning (PRL), to assess sensitivity to negative and positive feedback, and progressive ratio (PR), to assess motivation. Conventional tasks (e.g., light/dark box, social interaction) were also used to further assess behavioural phenotype. On PRL, animals with and without AHN performed similarly, suggesting neurogenesis does not play a causal role in sensitivity to valenced feedback. Similarly, the PR data do not indicate a role for AHN in motivation, although there was some evidence that mice with AHN deficits exhibited higher motivation. These data will be compared to those on conventional tasks to obtain a full behavioural profile, and to determine whether AHN is implicated in some, but not other, aspects of mood.

2-Cluster-238 *Mesopontine cholinergic signaling influences stress responses affecting behaviour*

Ornela Kljakic[1], Helena Janickova[1], Kaie Rosborough[1], Sanda Raulic[1], Sara Matovic[2], Robert Gros[1], Lisa Saksida[3], Timothy Bussey[3], Wataru Inoue[3], Marco Prado[3], Vania Prado[3]

[1]Robarts Research Institute, University of Western Ontario, [2]Robarts Research Institute, [3]University of Western Ontario

Pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT) are heterogenous brainstem structures that contain cholinergic, glutamatergic and GABAergic neurons. Several neuropsychiatric disorders have been associated with degeneration of the cholinergic neurons in this brain region, however, the importance of PPT/LDT cholinergic signaling for cognitive and non-cognitive functions is poorly understood. Previous work suggested that PPT/LDT cholinergic neurons play a role in attention and other forms of higher-level cognition, however these studies used non-selective methods to kill cholinergic neurons. To test the role of acetylcholine in higher-

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level cognition, we selectively eliminated the vesicular acetylcholine transporter (VAChT) in the PPT/LDT to generate mice that have impaired cholinergic signaling without interfering with other brainstem cell types and co-transmitted chemicals. We tested these VAChT-deficient mice using conventional and touchscreen-based cognitive tasks and found that they had little to no impairments in many behavioural paradigms including attention, yet failed to perform in the spatial and cued forms of the Morris water maze (MWM). Interestingly, spatial memory and visual spatial learning were intact in VAChT-mutants, but touchscreen performance was affected by a stressor and mice had altered corticosterone levels after the MWM. These results suggest that attention and many other cognitive functions are not affected by the loss of PPT/LDT cholinergic signaling, but an altered stress response can influence cognitive performance in aversive tasks.

2-Cluster-239 *Optimization of the touchscreen-based visuomotor conditional learning task in mice*

Oren Princz-Lebel[1], David Wasserman[1], Miguel Skirzewski[2], Penny MacDonald[2], Timothy Bussey[2], Lisa Saksida[2]

[1]Western University, [2]University of Western Ontario

The failure to effectively translate findings between animal and human studies - referred to as the 'translational gap' - is a longstanding yet largely unresolved problem in the study of cognition. This discrepancy is due in part to differences in how cognition is assessed in animal models and humans, including clinical populations. Many psychiatric and neurodegenerative diseases involve changes in the nature of stimulus-response (S-R) learning. In this field, the translational gap is exacerbated by differences in methods used to assess the acquisition and performance of habitual behaviour across species, leading to poor cross-species translation and often conflicting results. As a result, we set out to optimize a S-R learning task in mice with better translational potential. To achieve this aim, we used the touchscreen method, which allows identical tests to be given to mice and humans. Developed initially for rats, the Visuomotor Conditional Learning (VMCL) task encourages animals to learn arbitrary associations between visual stimuli and motor responses. In naïve C57BL/6 mice, we sought to optimize VMCL task parameters to promote more efficient responding, identifying the length of inter-trial intervals and the limited hold period as two potential candidates. The validation of this task will provide a novel means through which to study the neural correlates of S-R learning and will be used in conjunction with fiber photometry to understand the profile of dopamine responses in the striatum and related structures during the acquisition and performance of S-R rules.

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2-Cluster-240 *Integration of high-throughput touchscreen tasks and an open access database to evaluate cognitive dysfunction in mouse models of neurodegenerative diseases*

Flavio Beraldo[1], Daniel Palmer[2], Sara Memar[3], David Wasserman[2], Roseane Franco[1], Keon Coleman[1], Shuai Liang[4], Matthew Cowan[1], Robert Bartha[5], Stephen Strother[4], Boyer Winters[6], Lisa Saksida[1], Vania Prado[1], Timothy Bussey[1], Marco Prado[1]

[1]University of Western Ontario, [2]Western University, [3]Robarts Research Institute/BrainsCAN, [4]Rotman Research Institute, [5]Robarts Research Institute, [6]University of Guelph

Open Science has changed biomedical research by making research tools and results accessible and shareable, in order to accelerate and disseminate knowledge. This revolution has not yet started in mouse cognitive studies, which are critical for understanding the biological basis of neurodegenerative and psychiatric disorders. The behavioural techniques used to assess most of cognitive constructs remain unstandardized, limiting comparisons between studies and strains. The automated touchscreen behavioural tests provide a potential solution, enabling high-throughput approaches for systematic cognitive assessment with standardized outputs. Here we present an integration of touchscreen cognitive testing in several mouse models of neurodegenerative diseases, including mutations associated to Alzheimer's disease (AD), Parkinson's disease (PD) and Frontotemporal dementia/Amyotrophic Lateral Sclerosis (FTD/ALS) with an open-access database (mousebytes.ca). Mousebytes is integrated with an automated quality control and enables data storage, interrogation and comparison of mouse cognitive performance. Analysis of hundreds of mice suggest that different types of protein misfolding in AD, PD and ALS/FTD mouse models generate specific cognitive deficits. We envision that this new platform will represent significant advances in terms of high-throughput standardized open behavioural assessment and data sharing. The wide accessibility of touchscreen translational cognitive data in MouseBytes will help to increase replicability/reproducibility and aid the translation from bench to bedside.

2-Cluster-241 *The role of astrocytes in memory: focus on pattern separation*

Cecilia Kramar[1], Valeriy Ostapchenko[1], Olivia Reshmi Ghosh-Swaby[1], Vania Prado[1], Marco Prado[1], Tim Bussey[1], Lisa Saksida[1]

[1]University of Western Ontario

Pattern separation (PS), a cognitive function dependent on adult born neurons (ABNs) in the dentate gyrus (DG), involves the transformation of representations of distinct features into unique, less overlapping representations, minimizing interference. As it has recently been shown that astrocytes play a leading role in helping ABNs to integrate and function in DG networks, we hypothesized that astrocytes could play a role in regulating PS, and therefore provide a potential

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therapeutic target for treating brain diseases. To test this hypothesis we will manipulate astrocytes by expressing excitatory DREADDs specifically on astrocytes by crossing GlastcreERT2 mice with floxed hM3-Gq-DREADD mice. We will surgically implant cannulas into the DG of each mouse, allowing us to inject clozapine-n-oxide (CNO), or vehicle, directly into the DG. By immunofluorescence we were able to determine the expression of DREADDs on astrocytes, and a lack of DREADDs expression on ABNs or mature neurons. We also validate that DREADDs are functional by performing in vitro experiments with astrocytic cultures from these animals and measuring Ca+ levels after CNO induction. We have two main approaches for the study of PS: Spontaneous Location Recognition (SLR); and the touchscreen-based Location Discrimination (LD) task. We found that activation by CNO of the excitatory Gq-DREADDs on the astrocytes of the DG region improved PS performance in both the SLR and LD tasks. The results presented here will open up new areas of research in the emerging field of neuronal-astrocyte communication and cognition

IBRO

2-IBRO-242 *Rapid-onset anti-depressant-like potential of xylopic acid in mice and zebrafish*

Robert Biney[1], Charles Benneh[2], Donatus Adongo[2], Eric Woode[3]

[1]University of Cape Coast, [2]University of Health and Allied Sciences, [3]Kwame Nkrumah University of Science and Technology

Depression affects over 350 million people worldwide. Current antidepressants have slow onset of action while some patients are refractory hence a need for novel compounds with better antidepressant effects. Xylopic acid (15-β-acetoxy-16-ene-19-oic acid) was assessed for antidepressant effects with, open space swim test (OSST), LPS-induced depression test, tail suspension (TST) and forced swim tests (FST) in mice after daily oral doses of 3, 10 and 30 mg kg-1. It was also assessed using chronic unpredictable stress (CUS) model in adult zebrafish at doses of 1, 3 and 10 µM. Xylopic acid significantly reduced immobility in TST and FST ($p<0.001$). It showed faster onset of antidepressant action in the repeated OSST compared to fluoxetine and produced dose-dependent and significant reversal of immobility from the first day of treatment. It also showed anti-depressant-like effect against LPS-induced depressive-like behaviors by reducing anhedonia, increasing social interaction and also attenuating comorbid-anxiety associated phenotypes by decreasing rostral grooming. In zebrafish, xylopic acid reversed CUS-induced depression-like symptoms by increasing time spent in top segment of novel tank, reducing scototaxis and enhancing social interaction. These effects were abolished by antagonizing serotonergic and glutamatergic but not noradrenergic pathways using p-chlorophenylalanine and methysergide, alpha-methyl-p-tyrosine, and D-cycloserine. These results show a rapid antidepressant-like potential of xylopic acid in mice and teleost models for antidepressants.

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2-IBRO-243 *Comparison of outcome profiles between endoscopic third ventriculostomy (ETV) and ventriculoperitoneal shunt (VPS) in Malawian children diagnosed with hydrocephalus*

Tuntufye Mwambyale[1], Patrick Kamalo[2]

[1]College of Medicine, University of Malawi, [2]Blantyre Institute of Neurological Sciences

ETV is relatively new in the management of hydrocephalus, researchers have tried to find out its efficacy in the treatment of hydrocephalus and whether it gives comparable results to the standard of care treatment of VPS. In Malawi, there is minimal scientific research to determine the effectiveness of the ETV and VPS in the treatment of hydrocephalous. This study will be undertaken to measure the differences in the clinical, radiographical and biochemical presentation between endoscopic third ventriculostomy and ventriculoperitoneal shunt in Malawian children diagnosed with hydrocephalus in infancy. This is going to be achieved through neurodevelopmental assessment, measurement of the craniometrics parameters and biomarkers before treatment, at 6 months and subsequently after treatment for both procedures and comparison of the various parameters before and after treatment and between the two procedures. Data collection will occur through neurodevelopmental assessments done by trained occupational therapists using locally adapted clinical outcome measures to assess milestones before and after operations and in comparisons will be made. Head circumference and fontanelle status measurement shall be taken by clinicians. The fronto-occipital horn ratio and ventricle size measurements will be done on neuroimages taken before and after operation. CSF will be obtained from patients who will be treated for hydrocephalus during the shunt operations and analyzed for biomarkers such as amyloid precursor protein (APP) and derivative isoforms (sAPPα, sAPPβ, Aβ42), tau, phosphorylated tau (pTau), L1 cell adhesion molecule (L1CAM), neural cell adhesion molecule (NCAM-1), aquaporin 4 (AQP4), and total protein (TP) using enzyme-linked immunosorbent assay (ELISA).

2-IBRO-244 *Effect of exposure to a cholinergic receptor agonist on cognition in a prolonged febrile seizure rat model*

Cleopatra Rakgantsho[1], Gwladys Ngoupaye[1], Musa Mabandla[1]

[1]University of KwaZulu-Natal

Prolonged febrile seizures (PFS) are a paediatric condition that may lead to cognitive deficits later in life. The cholinergic system has been investigated in cognitive disorders with α7-nicotinic acetylcholine receptors (α7-nAchRs) modulating learning and memory and their agonists being shown to have pro-cognitive effects. In this study, PNU-282,987 (PNU), a selective α7-nAchR

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agonist was evaluated for its effect on PFS and on the learning and memory deficits associated with PFS in a rat model. PFS were induced in 14-day old Sprague-Dawley rat pups by administration of lipopolysaccharide (217 µg/kg), followed 2.5 hours later by kainic acid (KA, 1.83 mg/kg). PNU (10 mg/kg) was injected prior to KA administration while methyllycaconitine (MLA, 1 mg/kg), an α7-nAchR antagonist, was given following KA injection. Learning and memory function was assessed using the Morris water maze and the novel object recognition test. Acetylcholinesterase (AChE) and GDNF concentration in the prefrontal cortex and hippocampus were assessed using ELISA. α7-nAchR expression was assessed using western blot. The results show that PNU injection prevented PFS-associated learning and memory deficits. PNU inhibited the increase in AChE concentration and attempted to restore GDNF concentration in the hippocampus and in the prefrontal cortex. The agonist also prevented the increase in PFS-induced α7-nAchR expression. MLA injection inhibited the PNU effect. This suggests that the use of selective α7-nAchR agonists may be neuroprotective and hence preserve cognitive function following PFS induction.

Poster session 3: May 25, 2019

A - Development

3-A-1 *The RB family instructs multiple aspects of adult NSC fate*

Bensun Fong[1], Renaud Vandenbosch[1], Joseph Bastasic[1], Smitha Paul[1], Ruth Slack[1]

[1]University of Ottawa

The therapeutic potential for endogenous repair through experimentally-augmented neurogenesis is confounded by ongoing ambiguity regarding fundamental mechanisms governing neural stem cell (NSC) fate: balancing quiescence with activation, self-renewal with differentiation, and guiding commitment and survival. Here, we demonstrate a novel cell cycle-independent regulatory requirement for the Rb Family - pRb, p107 and p130 - in instructing multiple aspects of adult NSC fate. Employing an inducible mouse model, we demonstrate that Rb Family deletion (Rb-TKO) localized to the NSCs of adult mice results in a dramatic eight-fold expansion of the NSC population, four weeks post-induction. However, characterization both in vitro and in vivo reveals that these continuously-proliferating NSCs are unable to terminally differentiate, ultimately resulting in total niche exhaustion, eight weeks post-induction. Employing RNA-Seq of FACS-isolated NSCs from adult and developing Rb-TKO mice, we reveal a dramatic downregulation of genes and gene pathways associated with neuronal differentiation, with a distinct impact on adult-

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born neuronal commitment, as validated by qPCR and ChIP. Together, these findings demonstrate a novel regulatory requirement for the Rb Family in mediating the expansion, differentiation and long-term maintenance of adult NSCs. The goal of this study is to uncover methods of harnessing the machinery regulating NSCs, with the ultimate aim of restoring the afflicted brain during development and adulthood. This research is supported by a CIHR Grant to RSS.

3-A-2 *The role of different subpopulations of early- and adult-born granule cells in olfactory bulb functioning*

Sarah Malvaut[1], Tiziano Siri[1], Armen Saghatelyan[2]

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

In the adult olfactory bulb (OB), granule cells (GCs) represent the most numerous cell population and play an important role in odor processing. Interestingly, 15% of the entire pool of GCs is renewed during adulthood through the process of adult neurogenesis. Hence, it is possible to differentiate, at least, between two distinct pools of cells: the populations of pre-existing and adult-born GCs. However, the functional contribution of each subpopulation of GCs in odor processing and different odor behaviors such as novel odor stimulation, go/no-go operant conditioning and olfactory fear conditioning remains unclear. Using in vivo two-photon calcium imaging and the expression of the immediate early gene cFos, we show that GCs subtypes are functionally distinct at the basal state and in response to different behavioral tasks. During odor processing, GCs' activity is also modulated by the inputs they receive from other brain regions. However, these connections remain to be further described. We are currently using anterograde trans-synaptic viral labelling to characterize the synaptic inputs contacting the population of both pre-existing and adult-born GCs. Using in vivo two-photon Ca2+ imaging we are also investigating the functional contribution of GCs to olfactory functioning and behavior, depending on their wiring with other brain regions.

3-A-3 *Clustered Protocadherins regulate Purkinje cell dendrite development and cerebellar motor-related functions*

Julie Marocha[1], Julie Lefebvre[1]

[1]The Hospital for Sick Children

The dendritic arbor of a cerebellar Purkinje cell (PC) is exuberant yet highly organized such that its branches are uniformly distributed with minimal self-overlap. PC dendrites are patterned by dendrite self-avoidance, where branches from the same neuron (isoneuronal) repel each other to maximize the sampling of inputs. We have shown that self-avoidance is regulated by the clustered

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Protocadherins (Pcdhs) encoded by a family of 58 genes divided into the alpha (a), beta (b) and gamma (g) clusters. Pcdhs impart PCs with distinct cell-surface identities through combinatorial isoform expression. Using mutant mice lacking one or multiple Pcdh clusters, we showed that members of Pcdha and -g clusters functionally interact to regulate PC dendrite self-avoidance. Loss of Pcdhas or -gs caused a similar magnitude of dendrite self-crossings, but loss of both clusters severely enhanced self-avoidance defects (Lefebvre et al., 2012; Ing-Esteves et al., 2018). To elucidate the cellular basis of dendrite self-avoidance, we analyzed PC arbor development. We find that Pcdhg mutant PCs have smaller arbors with a higher density of dendrites, suggesting deficits in isoneuronal branch retraction or repulsion. To test if these cellular defects result in deficits in cerebellar-dependent functions, we conducted behavioural assays. Pcdha/g mouse mutants display motor deficits in accelerated rotarod and gait assays. In conclusion, we demonstrate that molecular diversity from the Pcdha and -g clusters are essential for dendrite self-avoidance in PCs and cerebellar-dependent motor functions in mice.

3-A-4 *Role of autophagy in neuronal migration under normal and pathological conditions*

Cédric Bressan[1], Marina Snapyan[1], Dave Gagnon[2], Simon Labrecque[1], Johannes Klaus[3], Paul De Koninck[2], Stephen Robertson[4], Silvia Cappello[3], Armen Saghatelyan[2]

[1]CERVO Brain Research Centre, [2]Université Laval, [3]Max Planck Institute of Psychiatry, [4]Dunedin School of Medicine, University of Otago

Cell migration is ATP dependent process with dynamic morphological remodeling leading to the formation of protein aggregates and organelle damage. Here we evaluated the role of autophagy, a catabolic pathway that maintains cellular homoeostasis, and its link to energy level in neuronal migration. We used mouse rostral migratory stream as a model system and optically monitored autophagy and energy variations in neuroblasts. The ATP/ADP ratio dropped during migratory phases and recovered to its baseline level during stationary periods. Time lapse monitoring of autophagy also showed an active flux with increased density of autophagosomes during neuroblasts' stationary phases. Blocking AMPK, an energy level sensor and autophagy activator, or genetic impairment of autophagy in neuroblasts led to decreased cell migration. By contrast, blocking AMPK in autophagy-deficient neuroblasts had no effect on migration suggesting the involvement of energy levels in autophagy activation. We next asked if autophagy is altered in disorders linked to neuronal migration defects. Mutations in genes encoding for cadherin ligand/receptor DCHS1 and FAT4 lead to periventricular heterotopias in humans. We observed an impairment of autophagy in human organoids with mutated FAT4 and DCHS1 genes as well as alterations in the migration of mutated human progenitor cells concomitant to a decrease in the number of lysosomes. Altogether, we show that autophagy may be activated because of energetic needs and is required for cell migration under normal and pathological conditions.

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3-A-5 *Semaphorin3f is a novel regulator of retinal progenitor cell differentiation*

Rami Halabi[1], Carrie Hehr[1], Sarah McFarlane[1]

[1]University of Calgary

The mature neural retina contains seven differentiated cell types: retinal ganglion cells, amacrine cells, bipolar cells, horizontal cells, cone and rod photoreceptors and Mueller glia. These cell types are derived from a pool of retina progenitor cells (RPCs), which through the concerted and coordinated efforts of intrinsic and extrinsic factors, generate waves of sequential differentiation to form a functional, organized and laminated retina. We identified the secreted chemorepellent Semaphorin3fa (Sema3fa) as a novel extrinsic signalling molecule necessary for spatial genesis of a specific neuron type in the vertebrate eye. The presence of sema3fa mRNA in RPCs of the early temporal retina and larval ciliary marginal zone (CMZ) suggests an ongoing role in RPC dynamics. Through CRISPR mutagenesis, we analyzed global loss of sema3fa on retinogenesis using zebrafish (Danio rerio). While gross embryonic development is normal, spatially restricted impairments in cellular differentiation and genesis are found in mutant retinae. Specifically, a significant reduction in the number of amacrine cells of the temporal retina is observed, with no changes to other cell types, or nasal amacrine cell populations. Additionally, transcriptional organization of the CMZ is disrupted, evident by an expansion of both atoh7 and ccnd1 mRNAs through the entire CMZ. Overall, we have identified a novel role for Sema3fa in retinogenesis and uncovered a new layer of complexity within retinal development - spatially constricted neurogenesis. (support: Alberta Innovates, Bright Focus Foundation, CIHR)

3-A-6 *Optogenetics study of the impact of the microbiota on brain development and function in zebrafish larvae*

Mado Lemieux[1], Vincent Boily[1], Rachel Barr[1], Gabriel Byatt[1], Tessa Herzog[1], Hamza Seghouani[1], Radu Turcitu[1], Marie-Ève Paquet[1], Nicolas Derome[1], Sylvain Moineau[1], Paul De Koninck[1]

[1]Université Laval

It is becoming widely accepted that the intestinal microorganisms play a central role in health and disease of vertebrates. When the host encounters a physiological or environmental stress, the microbiota ecosystem equilibrium is altered. Since neuro-active molecules are produced by the gut microbiota, this dysbiosis may induce reversible or irreversible consequences on brain development and neural function, affecting mental health. To investigate the mechanisms of gut-brain communication, we are using zebrafish (ZF) larvae and optogenetics methods to probe brain development through the transparent larvae and manipulate gut microbiota. Our first goal is to compare the developmental profile of brain cells in ZF that are either germ-free (GF), obtained by

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sterilization of the eggs, conventionally raised (CR) or reconventionalized (sterilized eggs grown in the same egg water as the CR). We are using 2-photon imaging of transgenic ZF expressing fluorescent proteins in different populations of neurons or in microglia. To assess the impact of the microbiota on network activity, we are using ZF expressing a pan-neuronal calcium indicator. We also aim to manipulate specific strains of bacteria in the ZF gut to assess their impact on brain development. To monitor their growth and evolution in the gut, we are colonizing GF larvae with bacteria expressing fluorescent proteins. Learning more on the impact of the microbiota on circuit development and function may provide useful insights to understand better the gut-brain relationship, which might then be translatable to human health.

3-A-7 *The role of activator E2Fs in adult neural stem cell quiescence and activation*

Daniel O'Neil[1], Edward Yakubovich[1], Bensun Fong[1], Renaud Vandenbosch[1], Ruth Slack[1]

[1]University of Ottawa

Within the adult mammalian brain, neural stem cells (NSCs) are maintained in niches in a quiescent state. Activation of NSCs requires re-entry into the cell cycle for the pool to proliferate and commit to a neural fate, giving rise to newborn neurons. The canonical Rb-E2F pathway is not only key in overcoming the G1/S-phase block, but novelly appears to be required for activation. We hypothesise that activator transcription factors E2F1 and E2F3 regulate exit from a quiescent state in adult NSCs. The requirement of activator E2Fs was confirmed using a Nestin-driven CreERT2 to delete E2Fs1/3 targeting NSCs in adult mice. We show that loss of E2Fs1/3 cause a decrease in the number and proliferation of adult NSCs, who adopt a quiescent profile in both the subgranular and subventricular zones. We employed this model to further isolate subventricular zone-derived NSCs using a R26:EYFP reporter and analysed transcriptional profiles by RNAseq. Loss of E2Fs1/3 shift NSC transcriptomes towards one overlapping with a quiescent neural stem cell signature (Codega et al., 2014), further highlighting the requirement of activator E2Fs for initial activation. Future work will focus on the interplay between E2Fs1/3 and targets from RNAseq data as potential regulators of quiescence in adult NSCs. As maintenance of quiescent NSCs is a prerequisite for lifelong neurogenesis, this study aims to determine the therapeutic potential of targeting activator E2Fs to combat niche exhaustion associated with aging and/or neurodegenerative conditions. This research is supported by a CIHR grant to RSS.

3-A-8 *Morphological annotations of cerebellar interneuron diversity and implications for the clustered Protocadherins*

Wendy Wang[1], Julie Lefebvre[2]

[1]University of Toronto, [2]The Hospital for Sick Children

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Inhibitory interneurons (iINs) exhibit significant within-class heterogeneity in response to differential environmental cues. This heterogeneity is a key challenge for the classification of iINs. To identify principles of iIN development and diversification, we established genetic strategies for accessing a population of iINs in the cerebellar cortex (Molecular Layer Interneurons, MLIs). Using these methods, we reconstructed the morphologies of over 250 MLIs, including their complete dendritic and axonal arbors. We found that the MLIs cluster into two canonical subpopulations--basket cells and stellate cells--based on unsupervised analysis of 24 morphological features. The stellate cell population is further represented by a graded continuum of differences, suggesting cellular heterogeneity based on local cues. To identify factors that control MLI morphogenesis, we investigated the roles of cell-surface receptors. We found that the large family of clustered Protocadherin (Pcdhs) recognition molecules are critical for the survival and arborization of MLIs. Loss of Pcdhs during neuronal migration results in reduced survival of MLIs and profound alterations to neurite patterning. By contrast, deletion of Pcdhs at later developmental stages did not affect cell numbers, but led to similar morphology defects. Interestingly, stellate cells are preferentially affected by Pcdh deletion, further highlighting their dependence on environmental signals. Together, these results demonstrate that the Pcdhs regulate survival and neurite arborization of iINs during two windows of development.

3-A-9 *The adaptor protein p66Shc plays a key role in the neural differentiation of mouse embryonic stem cells*

Andrew Powell[1], Robert Cumming[1], Dean Betts[1]

[1]University of Western Ontario

P66Shc is a member of the ShcA family of adaptor proteins, a family of proteins known to have a critical role in developmental processes. Previous studies in which the entire ShcA locus, which encodes multiple isoforms, was deleted resulted in developmental abnormalities across multiple tissues and embryonic lethality. The p66Shc isoform has been highlighted as a potential contributor to neurodegenerative diseases but its role in brain development has not been fully explored. Recent evidence suggests, however, that it may have a role in early neural development. This work explores the effect of p66Shc deletion on mouse embryonic stem cell (mESC) neural differentiation. Under neural differentiation conditions, p66Shc-/- mESCs show increased viability, decreased levels of SOX1, a transcription factor specific to neural epithelial progenitors, and maintained levels of OCT4, a transcription factor associated with mESC self-renewal and pluripotency. Moreover, p66Shc-/- mESC exhibit highly heterogeneous morphology following neural differentiation compared to wild type cells, suggesting a wide range of non-neural cell fates. Together, these results suggest that loss of p66Shc expression results in maintenance of pluripotency and a failure of the cells to fully commit to neural lineages. Thus, p66Shc may play a critical role in early neural development and potentially adult neurogenesis.

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3-A-10 *Mitochondrial dynamics in the regulation of neural stem cell fate decisions.*

Mohamed Ariff Iqbal[1], Smitha Paul[1], Keir Menzies[1], Mary-Ellen Harper[1], Mireille Khacho[1], Ruth Slack[1]

[1]University of Ottawa

Throughout life, the mammalian brain maintains a population of multipotent neural stem cells (NSCs). The differential regulation of mitochondrial dynamics has been demonstrated during development and aging in various tissues and relies on fission and fusion machinery consisting of Optic atrophy 1 (OPA1) and Mitofusins 1&2 (MFN1&2). Studies suggest a critical role for both mitochondrial dynamics and function in NSC maintenance and fate determination. Mitochondrial fragmentation is seen during aging and at an accelerated rate in neurodegenerative diseases. Recent studies have shown that experimentally-enhanced mitochondrial function improves the regenerative capacity of NSCs in aging tissues. Presently, little is known regarding the function of mitochondrial dynamics in the regulation of adult NSCs. We hypothesize that Opa1 is required to maintain the adult NSC pool, and disruption of Opa1 function will cause NSC depletion leading to cognitive impairment. Using a Tamoxifen-inducible Opa1-knockout targeting the adult NSC population, we find that Opa1 deletion results in impaired adult neurogenesis, accompanied by defects in learning and memory. We further examined the metabolic consequences of Opa1 deletion in NSCs and how that impacts on mitochondrial signaling, including ATP, NAD+, and ROS levels. We found Opa1 disruption results in NAD+ depletion, elevated ROS levels, which ultimately impact NSC fate decisions. In this study, we will address how metabolic regulation controls stem cell fate decision and potential therapeutic strategies. Supported by a CIHR grant to RSS.

3-A-11 *BDNF gene network, prenatal adversity and cognitive developmental trajectories in young children*

Euclides José de Mendonca Filho[1], Barbara Barth[2], Michael Meaney[2], Patricia Silveira[2], Patricia Silveira[2], Denise Ruschel[2]

[1]Universidade Federal do Rio Grande do Sul, [2]McGill University

Previous studies focused on the relation between prenatal conditions and neurodevelopmental outcomes later in life, but few have explored the interplay between genetics and prenatal adversity conditions on cognitive development. We aimed to analyze the interactions between a polygenic score for the Brain-derived Neurotrophic Factor gene network (BDNF ePRS) and a prenatal adversity score on cognitive developmental trajectory. A score based on genes co-expressed with the pre-frontal cortex BDNF was created using the effect size of the association between the individual SNP gene expression (GTEx). Prenatal adversity was evaluated considering several

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variables from the fetal environment. Cognitive function of 386 young children from the MAVAN cohort were assessed longitudinally in 3 time points (6, 12 and 18 months) using the Bayley-II mental scales. We used Item Response Theory to conduct concurrent vertical scaling of Bayley's mental abilities items to obtain scaled interval-level measures of mental development from the different age-related booklets. Linear mixed-effects modeling indicated that BDNF ePRS was negatively associated (β =-4.41, $p<0.05$) with cognitive development trend, BDNF ePRS and prenatal adversity interaction (β =3.19, $p<0.05$) reflects a steeper negative trend of cognitive development as function of adversity levels. Cognitive development trajectories seems to be influenced by the interplay between prenatal environment conditions and the expression of an important gene network that guides growth and differentiation of neurons and synapses.

3-A-12 *Characterization of Fragment C-driven msx3 expression in dorsal radial glia in the context of neural tube development*

Shea Keil[1], Anabelle Morissette[1], David Zheng[1], Ben Lindsay[1], Marie-Andrée Akimenko[1], Tuan Bui[1]

[1]University of Ottawa

Zebrafish are a useful model for vertebrate central nervous system (CNS) development since their embryos are transparent, genetic manipulations are easily generated, and the presence of conserved gene expression. Muscle segment homeobox 3 (msx3) is a conserved gene amongst vertebrates involved in patterning of the developing neural tube. Two short, highly conserved sequences upstream of msx3 in zebrafish and mice were identified. A 2kbp sequence from the zebrafish genome denoted Fragment C containing these conserved sequences was cloned upstream of the fluorescent protein EGFP, and this DNA construct was injected into zebrafish embryos. Fragment C was observed to drive expression of eGFP in the dorsal radial glia of the spinal cord beginning at 15 hours post fertilization and persisting into adulthood. Since radial glia are progenitors in the CNS of zebrafish that give rise to neurons and glia, and guide the migration of neurons during development we sought to determine the importance of msx3 expression in dorsal radial glia in zebrafish spinal cord development by removing the Fragment C enhancer. Using the CRISPR-Cas9 genome-editing system, the Fragment C enhancer was deleted from the zebrafish genome, and fish homozygous for this deletion were generated. In these fish, the rate of somite formation is reduced, indicative of a delay in embryonic development. Understanding the mechanisms by which msx3 is expressed in the zebrafish neural tube during development may elucidate the contribution of conserved molecular pathways to vertebrate central nervous system development.

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3-A-13 *The ultrastructure and connectivity of C. elegans motor neurons across developmental remodelling*

Ben Mulcahy[1], Daniel Witvliet[1], James Mitchell[2], WanXian Koh[1], Maggie Chang[1], Peter Bermant[2], Douglas Holmyard[1], Richard Schalek[2], Jeff Lichtman[2], Andrew Chisholm[3], Aravinthan D.T. Samuel[2], Mei Zhen[1]

[1]Mount Sinai Hospital, [2]Harvard University, [3]University of California, San Diego

After C. elegans hatches, it embarks on a period of postembryonic development where the motor circuitry is dramatically remodelled. Body motor neurons expand from 22 neurons (three classes), to 69 neurons (seven classes) through postembryonic neurogenesis. One of the pioneer motor neuron classes reverses polarity by converting their axons to dendrites, and vice versa. Throughout all stages of development, C. elegans is capable of coordinated locomotion. To investigate the strategies used by a neural circuit to complete a major remodelling event without compromising circuit output, we used serial section electron microscopy to reconstruct entire motor neurons at sequential stages of development. We traced motor neuron connectivity across the remodelling period, observing neurite outgrowth, presynaptic assembly and disassembly, and the acquisition of dendritic input. Our observations suggest a strategy where newly born neurons grow out their neurites and assemble presynaptic specializations concomitantly, using existing structures as temporary scaffolds. The sequence of presynaptic assembly differs between neuron classes, and the subsequent acquisition of postsynaptic input occurs through generation of dendritic spines in some neuron classes. There is also an intermediate period where the ultrastructural wiring of the motor circuit is disrupted, suggesting that structural wiring precedes functional wiring. Mechanisms for this may include delayed recruitment of postsynaptic receptors. We are currently investigating this possibility.

3-A-14 *Investigating the role of RNA-binding protein hnRNP-K in asymmetric neural precursor cell divisions of the developing cerebral cortex*

Julia Brott[1], John Vessey[1]

[1]University of Guelph

This study aims to investigate the temporal and spatial expression of RNA-binding protein heterogeneous nuclear ribonucleoprotein K (hnRNP-K) throughout cortical development, as well as the effect of hnRNP-K knockdown on cortical expansion. Immunocytochemistry was conducted on primary neural precursor cells (NPCs), in conjunction with immunohistochemistry on embryonic brain slices, in order to determine the neural cell types that express hnRNP-K, as well as its distribution throughout the cortex. hnRNP-K was positively identified in both precursor and post-mitotic stained neural cell types, and was observed to be equally distributed across the cerebral cortex. Western blotting using whole brain lysates collected at staggered timepoints

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throughout embryonic cortical development were used to quantify the expression of hnRNP-K throughout murine corticogenesis. Densitometry analysis revealed that hnRNP-K is constantly expressed throughout development when normalized to a constitutively expressed loading control. The in vitro effect of hnRNP-K knockdown on the production of various neural cell types will be assessed using primary NPCs from an embryonic CD1 mouse model. Additionally, co-immunoprecipitation will be used to identify protein binding partners of hnRNP-K to elucidate a possible mechanism of action. Knockdown is expected to result in an abnormal shift in the cell populations produced by asymmetric NPC divisions. Collectively, these experiments will demonstrate that hnRNP-K is not only expressed throughout, but required for proper embryonic cortical development.

3-A-15 *Adult-born neurons inhibit developmentally-born neurons*

Alyssa Ash[1], Timothy O'Leary[1], Erin Chahley[1], Desiree Seib[1], Jason Snyder[1]

[1]University of British Columbia

Recent reports indicate that lateral inhibition plays a powerful role in selecting which dentate gyrus (DG) neurons are recruited during memory formation. This raises the question of whether developmentally-born and adult-born DG neurons have distinct roles for inhibition, particularly in vivo when neuronal ensembles are selected during memory encoding. To address this we combined chemogenetics and immunohistochemistry for BrdU+Fos to silence and measure activity in developmentally and adult-born neurons as rats learned a spatial water maze task. Specifically, retrovirus was injected into the DG of male rats at 6 weeks of age to express the inhibitory DREADD receptor, HM4Di, in neurons born in adulthood. The same rats were also injected with BrdU to label developmentally or adult-born neurons. At 10 weeks of age rats were injected with either the HM4Di agonist CNO or vehicle, then trained in the water maze (8 trials). We found that silencing a subset of adult-born neurons (aged 4 weeks) increased activity levels in the developmentally-born neuron population. However, silencing adult-born neurons did not affect activation in other adult-born neurons within the DG, suggesting limited interaction amongst the adult-born population. We are currently looking at activation of interneurons (PV+ and SST+) within each treatment group to determine if silencing adult-born cells impacts downstream activity in inhibitory interneurons. Preliminary findings implicate PV+ interneurons in the modulatory sub-circuit between neuron populations within the DG.

3-A-16 *Representing neural reconstructions as cyclic graphs allows investigation of contact-dependent models of dendrite self-avoidance*

Samantha Ing-Esteves[1], Roozbeh Farhoodi[2], Julie Lefebvre[3]

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[1]University of Toronto / SickKids, [2]University of Pennsylvania, [3]The Hospital for Sick Children

During development neurons produce excess branches that are selectively pruned, but the mechanisms that regulate this selection are poorly understood. One mechanism of dendrite patterning is called dendrite self-avoidance, where dendrites originating from the same cell (self-dendrites) minimize overlaps. Previously we showed that the clustered Protocadherin (Pcdhs) regulate neurite self-avoidance. Based on studies showing that Pcdhs form transmembrane multimers that interact homophilically, we hypothesize that self-avoidance is mediated by Pcdhs interacting in trans across self-dendrites, providing a molecular mechanism for neurites to sense neighbouring branches during development. To test this, we acquired time-lapsed 3D volumes of developing retinal interneurons. We observed that transient self-contacts create dendritic bridges, defined as short orthogonal projections that connect self-dendrites. These bridges create closed-loops within the arbour. Morphological analysis requires neuron reconstruction, but conventional reconstructions are coded as SWC files that represent arbours as acyclic graphs. This prevents encoding of close-loops (cyclic graphs) in our dataset. Here we propose using integer linear programming to produce time-varying cyclic graphs from sets of experimentally acquired detections (nodes). Comparison of wildtype and Pcdh-mutant bridge dynamics in cyclic graph reconstructions will reveal the role of Pcdhs in arbour development. Importantly, our cyclic reconstructions are essential to modernizing reconstruction encoding and sharing.

3-A-17 *The clustered Protocadherins control the survival and size of inhibitory interneuron populations in the developing brain.*

Candace Carriere[1], Wendy Wang[2], Anson Sing[1], Julie Marocha[1], Leonor Separi[1], Julie Lefebvre[1]

[1]The Hospital for Sick Children, [2]University of Toronto

The excitatory-inhibitory balance is established by the integration of inhibitory interneurons with highly-specific patterns in distribution, number, and synaptic targeting. In the mammalian forebrain, ~30% of GABAergic inhibitory interneurons are eliminated by a postnatal program of cell death that is modulated by neural activity. Here we show that the survival of GABAergic inhibitory interneurons is regulated by the clustered Protocadherins, a family of 58 cell-surface receptors encoded by three gene clusters (Pcdh-alpha, -beta, -gamma). Through combinatorial expression and homophilic binding, the Pcdhs provide extraordinary diversity and selectivity for cell-surface interactions during neuronal wiring. We have shown in the retina that the alpha- and gamma-Pcdhs regulate dendrite self-avoidance and interneuronal survival. To determine whether these roles extend to interneurons in the brain, we conditionally deleted the Pcdhg genes from broad classes of GABAergic cells. Pcdhg; Gad2Cre mutant mice have reduced numbers of inhibitory interneurons in multiple brain regions including the cortex and basal ganglia. Mature Pcdhg mutant mice display several motor deficits and seizures. Deletion of Pcdhgs in the target pyramidal cells has no effect on inhibitory cell loss, revealing a cell- or population-autonomous

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role for Pcdhs. We have identified key signalling pathways that coordinate Pcdh-dependent control of GABAergic interneuron number. Together these studies will yield new insights on the cell-cell interactions that adjust inhibitory population sizes in the developing brain.

B - Neural excitability, synapses, and glia: Cellular mechanisms

3-B-19 *KCC2 manipulation alters features of migrating interneurons in ferret neocortex*

Francis Djankpa[1], Fritz Lischka[2], Mitali Chatterjee[2], Sharon Juliano[2]

[1]School of Medical Sciences, University of Cape Coast PMB, [2]Uniformed Services University of the Health Sciences

KCC2 is a brain specific chloride-potassium cotransporter affecting neuronal development including migration and cellular maturation. It modulates chloride homeostasis influencing the switch of GABA from depolarizing to hyperpolarizing, which contributes to the cues that influence the termination of neuronal migration. The expression of KCC2 during migration of interneurons, therefore, correlates with the ability of these cells to respond to GABA as a stop signal. Manipulation of KCC2 in development can affect various aspects of migrating neurons, including the speed. We describe the effect of KCC2 downregulation and inhibition on features of migrating interneurons of normal ferret kits and those treated with methylazoxymethanol acetate (MAM), which increases KCC2. Treatment of organotypic cultures with Bisphenol A (BPA), an environmental toxin that alters gene expression, also downregulates KCC2 protein. In organotypic slices treated with the KCC2 antagonist VU0240551, chloride imaging shows inhibition of KCC2 via blockade of chloride flux. Time-lapse video imaging of organotypic cultures treated with either drug, shows a significant increase in the average speed, step size, and number of turns made by migrating neurons leaving the ganglionic eminence. Our findings reveal the harmful effect of environmental toxins on brain development and potential consequences in the pathogenesis of neurodevelopmental disorders.

3-B-20 *Investigating a potential activator of spreading depolarization released by stressed gray matter.*

Nikita Ollen-Bittle[1], Kelly Lee[1], Michael Fisher[1], Peter Gagolewicz[1], David Simon[1], Richard Oleschuk[1], Albert Jin[1], R David Andrew[1]

[1]Queen's University

Stroke, head trauma and cardiac arrest each result in ischemic insult to the brain, causing failure of the Na/K pump within two minutes wherever blood flow is completely compromised. Without reperfusion, gray matter undergoes a terminal spreading depolarization (SD) but in partially

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perfused tissue SD can recur, expanding neuronal injury over ensuing hours and days. The molecular events linking ischemia, pump failure and SD initiation/propagation are not well understood. Based on previous work in our lab, we suspect that the Na/K pump converts into an open channel which drives SD (Gagolewicz & Andrew, SFN Abstract, 2017). In the current study, 8 live coronal rat brain slices were incubated in oxygen/glucose deprived saline (OGD, 35°C, 10min). Slices were removed, oxygen and glucose rebalanced, and the saline superfused over a naïve slice at 35°C. SD was evoked in ~60% of naïve slices. Alternatively SD was induced in 8 slices by brief hyperthermia (40°C, 10min). Saline taken and superfused elicited SD in ~70% of naïve slices. Analysis post-SD showed that superfusate potassium was only elevated by <2mM. We propose that a SD activator (SDa) released from OGD- or hyperthermia-exposed slices induces SD in the non-stressed slice. We are analyzing the incubate of the 8 slices (sampled pre- and post-SD) using liquid chromatography, mass spectroscopy and MALDI to further characterize a hypothesized SDa. Release of a SD activator by compromised gray matter in response to ischemia could mediate both the initiation and self-propagation of SD.

3-B-21 *tLTD requires presynaptic NMDAR-mediated JNK signalling*

Jennifer Brock[1], Per Jesper Sjöström[1]

[1]McGill University

NMDA receptors (NMDARs) are widely believed to function as coincidence detectors in Hebbian plasticity. To serve this function, they need to be situated postsynaptically, yet presynaptic NMDARs (preNMDARs) have been reported for decades. PreNMDARs elicit timing-dependent long-term depression (tLTD) at connections between neocortical layer-5 (L5) pyramidal cells (PCs), but the signalling path is unknown. We recently showed that preNMDARs differentially regulate spontaneous and evoked release via c-Jun N-terminal kinase-2 (JNK2) and Rab3-interacting molecule-1 (RIM1) signalling, respectively. Consequently, we explored if tLTD also depended on either of these paths. Synaptically coupled L5 PCs were patched in acute visual cortex slices from P11-P16 mice, with L5 PCs identified post hoc by 2-photon microscopy. RIM1 was conditionally knocked out (KO) by crossing with Emx-Cre mice. C57BL/6J mice served as wildtype (WT). JNK2 was blocked with SP600125 (4 μM). tLTD was induced at 20 Hz with -25 ms temporal difference. We obtained the same tLTD magnitude in WT (65% ± 5%, n = 9) and RIM1 KO mice (65% ± 7%, n = 4, p = 0.95; pooled: $p < 0.001$ vs control, 65% ± 4%, n = 13). In both cases, tLTD was presynaptic by analysis of coefficient of variation and paired-pulse ratio. However, SP600125 abolished tLTD (96% ± 2%, n = 8, p = 0.34 vs control). In conclusion, tLTD relies on JNK but not RIM1 signalling. Since JNK mediates non-ionotropic preNMDAR control of spontaneous release, this suggests that tLTD too may depend on this unconventional form of NMDAR signalling.

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3-B-22 *Transcriptional and translational regulation at the early and chronic phases of neuropathic pain*

Sonali Uttam[1], Marc Parisien[1], Seyed-Mehdi Jafarnejad[2], Mehdi Amiri[1], Francis Beaudry[3], Luda Diatchenko[1], Arkady Khoutorsky[1]

[1]McGill University, [2]Queen's University Belfast, [3]Université de Montréal

Acute pain serves as a protective mechanism, guiding the organism away from actual or potential tissue injury. In contrast, chronic pain is a debilitating condition without any obvious physiological advantage. This suggests that the transition to, and the maintenance of chronic pain rely on different gene expression patterns to support biochemical and structural changes within the pain pathway. Gene expression can be regulated at various levels including transcription and translation. While transcriptomics in pain is widely studied, there have been only very few studies aimed at identifying translationally regulated genes. Regulation of mRNA translation has emerged as an important step in the control of protein expression in the cell. However, mRNAs whose translation is altered in different stages of chronic pain remain largely unknown. In this study, we performed genome-wide translational profiling using Ribosome footprinting in parallel with transcriptional profiling using RNA-Seq and proteomics of dorsal horn of the spinal cord in a mouse model of neuropathic pain, spared nerve injury (SNI). We performed this multi-level gene expression profiling at early (day 4) and late (day 63) time points to investigate the differences in patterns of gene expression between the induction and maintenance stages of chronic pain. Interestingly, preliminary analysis shows that, while both transcriptional and translational regulation are exerted in the early stage, transcriptional regulation subsides by the late stage, and a new pattern of translation emerges.

3-B-23 *Neocortical potassium redistribution in vivo is influenced by neuronal/synaptic activity, pannexin channels, and astrocytic gap junctional communication*

Azin Ebrahim Amini[1], Bojana Stefanovic[2], Peter Carlen[3]

[1]UHN, [2]Sunnybrook Research Institute, [3]Krembil Research Institute

Cerebral extracellular potassium ion concentration ([K]e) is tightly regulated and has a major impact on brain functionality. [K]e is elevated during stroke, anoxia and epilepsy. K redistribution is little studied area. Most studies were limited to measuring from a single spot and few are done in vivo. Based on a well-developed experimental platform, this study is designed to elucidate the factors contributing to [K]e redistribution in the neocortex. 2 double-barrelled K-sensitive electrodes, each coupled with a local field potential (LFP) electrode, were placed about 3 mm apart in mouse neocortex to acquire in vivo signals. 50mM KCl solution was injected focally beside one of the K-LFP electrodes; [K]e and LFP were measured before and after topical application of a drug. We observed that the response to focally injected K, measured beside the K injecting

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electrode, was a transiently increased [K]e and a depolarization, which spread into neighbouring tissue, measured by the remote K-LFP electrode. The local raised [K]e response was decreased locally and remotely in the presence of astrocytic gap junction opening or pannexin channel blockade. The local [K]e response was increased or remained unchanged locally when astrocytic gap junctions or neuronal communication and activity were blocked respectively, whereas the [K]e responses measured from the remote K-LFP electrode were decreased remotely in both cases. Our results provide evidence of K redistribution in the neocortex which is partly mediated via astrocytic gap junctions, pannexin channels and neuronal/synaptic activity

3-B-24 *Classification of neuronal response patterns using machine learning and optimal feature sets: Linking in-vivo to in-vitro experiments*

Eric Kuebler[1], Milad Khaki[1], Michelle Jimenez[1], Jackson Blonde[2], Kelly Bullock[1], Florian Pieper[1], Roberto Gulli[3], Ben Corrigan[4], Lyndon Duong[1], Rogelio Luna[1], Gustavo Parfitt[1], Megan Roussey[1], Hiroyuki Igarashi[4], Julia Sunstrum[4], Sara Matovic[1], Meagan Wie

[1]Robarts Research Institute, [2]Schulich School of Medicine and Dentistry, [3]Columbia University, [4]University of Western Ontario, [5]Western University, [6]Leibniz-Institut fur Primatenforschung

Scientists trying to understand higher brain functions and cortical computations have benefitted from two successful, yet, differentially limited experimental strategies. The first approach, in vivo extracellular recordings, offer a glimpse of the neuronal population and circuit dynamics that contribute to the behavior of animals. However, because responses vary widely across neurons and stimuli, it is often difficult to characterize what types of cells (i.e., pyramidal, interneuron) contribute to behaviour. The second approach, in vitro intracellular recordings, offer a view of the biophysical properties intrinsic to the cell; however, lacking the influence of circuits and sensory input. Unfortunately, no successful bridging between these two methods exists (i.e., cell type classification of neurons recorded in vivo based on what is observed during in vitro recordings of the same brain area). This is remarkably unfortunate for our closest analog the non-human primate (NHP) because they are vital in experiments investigating complex behaviors. Bridging in vivo and in vitro experiments is central to our understanding of the structure and function of brain circuits. Here, we utilize in vivo extracellular and in vitro intracellular electrophysiology, paired with machine learning methods, to investigate circuit structure and function. Importantly, bridging between in vivo and in vitro experiments may allow us to understand how single neurons and circuits contribute to function in the awake brain.

3-B-25 *Modelling and classification of travelling wave dynamics in the visual cortex*

Lawrence Oprea[1]

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[1]McGill University

During ocular transit (saccades) we become effectively blind as processing of motion-blurred images is suppressed in the visual system. Optical tracking experiments in macaques have shown that travelling waves of electrical activity occur in the visual brain area V4, after a saccade event. These waves increase visual sensitivity and therefore may help alleviate suppression. We have created a neuronal network model to probe the rapid dynamics of wave initiation and interaction with the neuronal substrate. The network neurons are coupled using Gaussian kernels with which the inhibitory/excitatory balance is varied. Fast switching occurs between wave and synchronous states through the modulation of this kernel. We classify the resultant wave dynamics using a machine learning approach and optical flow analysis that allows models of any dimensionality to be analyzed as 2D flows.

3-B-26 *Glutamatergic synapse potentiation is associated with neuroendocrine sensitization to stress*

Julia Sunstrum[1], Eric Salter[2], Wataru Inoue[1]

[1]University of Western Ontario, [2]University of Toronto

Chronic stress can sensitize the hypothalamic-pituitary-adrenal (HPA) axis-the neuroendocrine branch of the stress response. However, the underlying mechanisms for this plasticity remain unknown. The activation of the HPA axis relies on the release of corticotropin releasing hormone (CRH) from neuroendocrine neurons in the paraventricular nucleus of the hypothalamus (PVN). Here, using slice patch clamp electrophysiology, we found that glutamatergic synaptic transmission to CRH neurons was potentiated after repeated stress in mice. Specifically, in CRH neurons from control non-stressed mice, pharmacological stimulation of cAMP signalling (either by activating adenylyl cyclase or blocking cAMP breakdown by phosphodiesterase) increased the frequency but not the amplitude of spontaneous excitatory postsynaptic currents (sEPSCs), indicating facilitation of glutamate release from the presynaptic terminals. Following repeated stress, this cAMP-mediated synaptic facilitation was exaggerated, suggesting that chronic stress sensitized glutamate synapses to cAMP-mediated facilitation of glutamate release. Furthermore, this cAMP-induced facilitation was dependent on presynaptic hyperpolarization-activated cyclic-nucleotide-gated (HCN) channels. This result identifies a possible mechanism that supports stress sensitization of the HPA axis and suggests a novel role for HCN channels in the PVN.

3-B-27 *Toward cellular-based explanations of LFP theta-gamma rhythm generation in the hippocampus*

Alexandra Chatzikalymniou[1], Frances Skinner[2]

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[1]Krembil Discovery Tower, [2]Krembil Research Institute

One of the most studied examples of cross-frequency coupling (CFC) in the rodent hippocampus, is the phase-amplitude coupling (PAC) of theta and gamma rhythms. CFC has been implicated in various cognitive roles and specific CFC changes may be an early biomarker for neurological disease. However, underlying cellular-based mechanisms are difficult to determine. This is largely because CFC analyses are done using population activity local field potential (LFP) recordings, and it is unclear how the cellular substrates generate PAC in LFPs. To obtain a cellular-based understanding of theta-gamma PAC, we leveraged insights from `simple' model mechanisms in application to biologically detailed models of the entire CA1 as based on a whole hippocampus preparation that spontaneously generates theta-gamma LFP rhythms. We built reduced, microcircuit models that represent one of the many individual network oscillators across the septo-temporal axis of the CA1. Besides CA3 and entorhinal cortical afferents, our models also include recently discovered inputs from the subiculum. Our reduced network models are able to exhibit theta-gamma LFP rhythms. Theta-gamma activity is dictated by excitatory-inhibitory interactions in the form of synaptic currents passing through excitatory cell membranes. Analysis of these simulations will allow us to extract cellular-based explanations of how PAC in theta-gamma LFP recordings arise and how external inputs modulate PAC in the hippocampus.

3-B-28 *Functional heterogeneity of human and mouse layer 5 pyramidal neurons*

Homeira Moradi-Chameh[1], Prajay Shah[1], Shreejoy Tripathy[2], Taufik Valiante[3]

[1]Krembil Research Institute, [2]University of Toronto, [3]Krembil research Institute, University Health Network

Intrinsic biophysical diversity in excitable cells manifests as differing spike outputs to similar current inputs despite the cells being of the same molecular class. Such functional heterogeneity is advantageous since it increases the information within a population of neurons. Despite there being clear evidence for functional heterogeneity in early sensory afferents, it is unknown whether the cortex also employs heterogeneity as a fundamental organizing principle. Methods: We performed in-vitro whole-cell recording of Layer 5 pyramidal cells from freshly excised tissue slices from patients undergoing epilepsy surgery for temporal lobe epilepsy and acute mouse brain slices. All experiments were performed with synaptic blockers. We recorded principle cell responses to an identical Gaussian filtered white noise current stimulus 2.5s long (n = 7 mouse and human cells each, 30 trials/cell). The noise variance (σ) was 10% and 20% of the direct current (25-200 pA; σ =20 and 40 pA) offset for each cell. Results: We observed lower pair-wise correlations between spike trains of different cells versus trials from the same cell. Linear decoding approaches estimate how well each cell's spike train encodes the input stimulus. The reconstructed stimulus operated on a mean timescale of 21.5ms +/- 9.2, but showed considerable heterogeneity amongst cells. Conclusion: These results suggest that functional heterogeneity is a

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property of both human and mouse cortical neurons. Such diversity may contribute to increased overall information representation within cortical circuits.

3-B-29 *Sag is a major contributor to human pyramidal cell intrinsic diversity across cortical layers and between individuals*

Homeira Moradi Chameh[1], Lihua Wang[1], Alvin Lee[2], Bushra Shehzad[2], Liang Zhang[3], Peter Carlen[1], Shreejoy Tripathy[2], Taufik Valiante[4]

[1]Krembil Research Institute, [2]University of Toronto, [3]University Health Network, [4]Krembil research Institute, University Health Network

Background: The hyperpolarization-activated non-specific cation current, Ih, greatly shapes a neuron's subthreshold integrative properties. Here, we wanted to understand how Ih and other intrinsic features contribute to the electrophysiological diversity of superficial (L2/3) and deep layer (L5) pyramidal neurons in the human neocortex. Methods: In vitro whole-cell recordings were obtained from 214 pyramidal neurons in unaffected cortical tissue from 51 patients undergoing neurosurgery for temporal lobe epilepsy or tumor resection. We validated our results in a second dataset of 413 neurons collected by the Allen Institute for Brain Sciences. Results: Human L5 pyramidal neurons had more prominent sag and larger Ih currents relative to L2/3 neurons. In addition, L5 neurons were more excitable, demonstrating rebound bursting, higher input resistances, and more depolarized resting potentials. Pharmacologically blocking Ih produced a larger change in membrane properties in L5 compared to L2/3 neurons and markedly reduced the observed cell-to-cell variability across cells. Although no peak in resonance was observed, we found that L5 neurons better tracked inputs at the delta and theta frequencies. Patient-level demographic features revealed larger sag amplitudes in older patients and those with tumors. Conclusion: Sag is a dominant feature of the human cortical microcircuit and is prominently expressed in L5 pyramidal cells. In addition, neuronal Ih is not a fixed feature of a cell type but instead dynamically changes due to a subject's disease state and over their lifet

3-B-30 *Presynaptic release probability scales with synapse size under basal conditions and during long-term potentiation*

Matthew MacDougall[1], Alan Fine[1]

[1]Dalhousie University

Synaptic specializations scale in proportion to key components of the synaptic microenvironment. For example, the number of postsynaptic AMPA-type glutamate receptors (AMPARs) scale with the size of postsynaptic densities (PSD), the size of presynaptic active zones (AZ) scale with the

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PSD, and transmitter release probability (pr) scales with AZ size. A widely held view in the field has been that synapses are made stronger via the peripheral incorporation of new AMPARs at the PSD. However, the possibility that receptor activation is largely restricted to a small central zone ("hotspot") within the PSD opposite functional release sites challenges this view. Using optical quantal analyses and Monte Carlo simulations we explore these relationships. We find that pr, but not potency, scales with estimates of synapse size. Furthermore, we show that pr increases with synapse size following the induction of long-term potentiation (LTP), that these increases in pr are maintained while LTP-associated spine enlargement is, on average, transient with negligible changes in postsynaptic potency. These data provide compelling support for the receptor hotspot hypothesis and demonstrate that presynaptic mechanisms do in fact accompany abrupt changes in spine morphology following the induction of LTP. What is more, these data cast considerable doubt on the prevailing view of postsynaptic expression of synaptic strength under basal conditions and in LTP. Under these experimental conditions, synaptic strength appears to be modulated chiefly via reliability, rather than potency, of transmission.

3-B-31 *Microglia prefer interneurons: a structural analysis of microglia-interneuron interactions in the CA1 hippocampus*

Etienne Gervais[1], Ana Claudia Gonçalves Bessa[1], Lisa Topolnik[1]

[1]Université Laval

While microglia has been consistently reported to interact with principal cells and, through control of synaptic elements, regulate their physiological function, much less is known about their partnership with GABAergic interneurons. Here, we analysed microglia interactions with parvalbumin- (PV+) and somatostatin-expressing (SST+) interneurons in the CA1 hippocampus of normal mice and mice carrying the APP/PS1 mutations associated with Alzheimer's disease (AD). We first uncovered a high level of interactions between the two cell types, with 98% of SST+ and 86% of PV+ cells receiving different types of microglial contacts. The latter included the soma-to-soma (4%), process-to-soma (58%) and process-to-dendrite (38%) contacts, which were similar in fraction between SST+ and PV+ cells in normal mice. Moreover, we found that microglial cells not only contacted almost every SST+ interneuron, but also made significantly larger areas of interaction for soma-to-soma and process-to-dendrite contacts with SST+ cells. In contrast, PV+ cells exhibited larger areas of interaction for process-to-soma contacts. Finally, despite a 25% loss in SST+ cells in 6-months old AD mice, microglia interactions with these cells remained unchanged. In contrast, PV+ cells, which survived in AD mice, showed a larger area of interaction for process-to-soma contacts, pointing to a selective microglia impact on PV+ interneuron activity in AD. In summary, these results reveal important structural interactions between microglia and inhibitory interneurons, which may be essential for interneuron function.

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3-B-32 *The C9orf72 repeat expansion associated with fronto-temporal dementia leads to synaptic dysfunction in hippocampal pyramidal neurons*

Alfonsa Zamora-Mortalla[1], Lisa Topolnik[1]

[1]Université Laval

Frontotemporal Dementia (FTD), a type of early onset dementia caused by degeneration of the frontal and anterior temporal lobes, leads to cognitive deficits and behavioral and language abnormalities. Recently, the C9orf72 GGGGCC expansion mutation has been reported as the most frequent genetic cause of FTD. In the present study, using the C9orf72 BAC expansion mouse model with ~500 repeats (C9-500) that presents the age-dependent neurodegeneration in the hippocampus, we examined whether the C9orf72 GGGGCC genetic repeat can be associated with synaptic dysfunction in hippocampal CA1 pyramidal neurons. We found significant changes in the amplitude and frequency of both excitatory and inhibitory miniature postsynaptic currents. Moreover, C9orf72 genetic repeat was not associated with changes in short-term plasticity but resulted in the increased NMDA/AMPA receptor ratio. The latter pointed to changes in long-term synaptic plasticity at CA3-CA1 connection in parallel with changes in network activity, which are currently under investigation. In summary, our data indicate that, in hippocampal CA1 pyramidal neurons, C9orf72 expansion mutation may lead to postsynaptic dysfunction via increased function of glutamatergic NMDA receptors. Ongoing detailed analysis of the synaptic dysfunction in C9orf72 BAC mouse model will reveal underlying mechanisms and consequences of synaptic pathology for hippocampal mnemonic processing and FTD pathogenesis.

3-B-33 *Dopamine D2 receptor/voltage-gated sodium channel interaction regulates D2-driven signaling and behavior*

Gohar Fakhfouri[1], Pavel Powlowski[2], Clémentine Quintana[2], Mohamed Chahine[1], Jean-Martin Beaulieu[2], Giulio Pergola[3], Antonio Rampino[3], Jivan Khlghatyan[1], Thomas Del'Guidice[1]

[1]Université Laval, [2]University of Toronto, [3]University of Bari

Lamotrigine curtails epilepsy by blocking voltage gated sodium channels (NaV). In addition, lamotrigine affects dopamine-related behavior & inhibits GSK-3β via a mechanism involving β arrestin 2 & dopamine D2 receptor (DRD2). However, lamotrigine is not a DRD2 ligand. We investigated possible interaction of DRD2 and NaVs. Biochemical & behavioral studies showed that lamotrigine affects DRD2 β arrestin-2 mediated Akt/GSK-3β but not DRD1 signaling in vivo. Translatome profiling in DRD2 neurons of stiatum and medial pre-frontal cortex (mPFC) revealed strong expression of NaV1.2 and NaV 1.6. Further characterization showed a co-localization of DRD2 and NaV 1.6 in striatal medium spiny neuron dendrites. Co-immunoprecipitation and BRET studies revealed a direct interaction between DRD2 and a portion of NaV1.6 C-terminal. Overexpression of this NaV1.6 domain in striatal DRD2 neurons abolished β arrestin mediated

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DRD2 signaling and locomotion, while in mPFC, it lead to working memory impairment. To investigate a potential NaV1.6/DRD2 interaction in humans we used the common mind database to identify a functional single nucleotide polymorphism affecting NaV1.6 expression in mPFC and investigate its interaction with a polygenic score for DRD2 expression. Study of 350 control subjects showed a strong interaction between DRD2 and NAV1.6 genetic variants in regulating working memory performance and associated fMRI signal. These data indicate the existence of a functional and physical interaction between NaV1.6 & DRD2 leading to negative modulation of D2R β arrestin-2 mediated signaling.

3-B-34 *Circadian rhythm of neuronal activity in vasopressin neurons of the suprachiasmatic nucleus in male and female rats.*

Zahra Thirouin[1], Claire Gizowski[2], Charles Bourque[2]

[1]Research Institute at McGill University Health Center, [2]McGill University

The hypothalamic suprachiasmatic nucleus (SCN) is known as being the site of the central circadian clock. It coordinates mammalian biological rhythm-controlled behaviors such as sleep/wake cycle. The SCN circadian rhythm is entrained to the daily light/dark cycle through synaptic inputs received from specialized retinal photoreceptors. The SCN is comprised mainly of GABAergic neurons that can be divided into subgroups according to the neuropeptide co-transmitter they express. Approximately 30% of SCN neurons express arginine vasopressin (AVP) and display pronounced daily fluctuations of AVP gene expression as well as cyclic peptide release into the cerebrospinal fluid. These may result from the light/dark cycle of action potential firing of SCN-AVP neurons. While it is known that the average firing frequency of these neurons is high around mid-day and low during nocturnal hours (Kalsbeek et al. 2010), the specific activity profile of SCN-AVP neurons has not been defined due to difficulties in obtaining targeted recordings from identified neurons. In this study, male and female adult AVPeGFP Wistar rats (Ueta et al. 2005) were housed under a 12:12h light/dark cycle, and we obtained cell-attached recordings from brain coronal slices. Our results show that SCN-AVP neurons in males and females have similar daily oscillations in firing rate and proportions of cells active as a function of time. However, the average maximum firing frequency was found to be higher in males compared to females.

3-B-35 *Transcriptomic correlates of electrophysiological and morphological diversity within and across neuron types*

Shreejoy Tripathy[1], Claire Bomkamp[2], Carolina Bengtsson Gonzales[3], Jens Hjerling-Leffler[3], Ann Marie Craig[2], Paul Pavlidis[2]

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[1]University of Toronto, [2]University of British Columbia, [3]Karolinska Institute

In order to further our understanding of how gene expression contributes to key functional properties of neurons, we combined publicly accessible gene expression, electrophysiology, and morphology measurements to identify cross-cell type correlations between these data modalities. Building on our previous work using a similar approach, we distinguished between correlations which were "class-driven," meaning those that could be explained by differences between excitatory and inhibitory cell classes, and those that reflected graded phenotypic differences within classes. Taking cell class identity into account increased the degree to which our results replicated in an independent dataset as well as their correspondence with known modes of ion channel function based on the literature. We also found a smaller set of genes whose relationships to electrophysiological or morphological properties appear to be specific to either excitatory or inhibitory cell types. Next, using data from Patch-Seq experiments, allowing simultaneous single-cell characterization of gene expression and electrophysiology, we found that some of the gene-property correlations observed across cell types were further predictive of within-cell type heterogeneity. In summary, we have identified a number of relationships between gene expression, electrophysiology, and morphology that provide testable hypotheses for future studies.

3-B-36 *Locus of potentiating effects of superoxide on synaptic plasticity*

Tatjana Golovin[1], Alan Fine[1]

[1]Dalhousie University

The role of reactive oxygen species (ROS) in biological systems is often studied in the context of their destructive characteristics, such as when ROS are produced in high concentrations during pathogen defense or in apoptosis. However, certain ROS, particularly superoxide and hydrogen peroxide, have been shown to contribute to synaptic plasticity when produced in specific low concentrations. Their extensive clearance either in the intra- or extracellular space in transgenic animals revealed impaired induction of synaptic plasticity in the form of long-term potentiation or depression (LTP or LTD, respectively). Previous studies also showed that while low concentrations of hydrogen peroxide intensify the effects of electrical induction of LTP or LTD if applied prior to induction, superoxide on its own has potentiating or depressing effects that are strictly coupled to physiologically relevant concentrations. Here we focus on identifying the locus of superoxide potentiation using whole-cell patch clamp recordings to analyze changes in the frequency and amplitude of miniature excitatory postsynaptic currents (mEPSCs), which are generally indicative of pre- and postsynaptic changes, respectively. Understanding the physiologically relevant actions of superoxide and its mechanisms will aid in understanding fundamental processes underlying synaptic plasticity in the healthy brain and may provide insights into the progression of neurodegenerative diseases, like Alzheimer's Disease.

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3-B-37 *Identification of a complex containing OGT-1 O-GlcNAc transferase and EEL-1 ubiquitin ligase that regulates GABA neuron function*

Andrew Giles[1], Muriel Desbois[1], Karla Opperman[1], Rubens Tavora[2], Marissa Maroni[1], Brock Grill[1]

[1]The Scripps Research Institute - Scripps Florida, [2]Florida Atlantic University

Inhibitory GABAergic transmission is required for proper circuit function in the nervous system. However, our understanding of molecular mechanisms that preferentially influence GABAergic transmission, particularly presynaptic mechanisms, remains limited. We previously showed the EEL-1 ubiquitin ligase preferentially regulates GABAergic presynaptic transmission [1]. To explore how EEL-1 functions, we performed affinity purification proteomics from C. elegans, and identified OGT-1 O-GlcNAc transferase as an EEL-1 binding protein. This is an intriguing observation as we know little about how OGT-1 affects neuron function. We confirmed the OGT-1/EEL-1 complex forms in neurons in vivo and showed that the human orthologs, OGT and HUWE1, also bind in cell culture. Like EEL-1, we found OGT-1 is expressed in GABAergic motor neurons, localizes to GABAergic presynaptic terminals and functions cell autonomously to regulate GABA neuron function. Consistent with OGT-1 and EEL-1 forming a multi-functional complex, genetic results indicate ogt-1 and eel-1 act in parallel to regulate GABA neuron function. Point mutation analysis indicated EEL-1 functions via ubiquitin ligase activity. In contrast, OGT-1 does not function via enzymatic glycosyltransferase activity. These results indicate that OGT-1 and EEL-1 form a conserved signaling complex and function to affect GABA neuron function [2]. [1] Opperman, Mulcahy, Giles, Risley, Birnbaum, Tulgren, Dawson-Scully, Zhen, Grill, 2017, Cell Rep. [2] Giles, Desbois, Opperman, Tavora, Maroni, Grill, under revision, J Biol Chem.

3-B-38 *Divergent roles of the Fragile X Mental Retardation protein (FMRP) in developmental remodeling of a central synapse*

Ankur Bodalia[1], Jason Arsenault[1], Lu-Yang Wang[1]

[1]The Hospital for Sick Children

During the critical period of development, excitatory synapses undergo rapid remodeling by changing the abundance and composition of postsynaptic receptors to enable fast neurotransmission. Dysregulation of this process, e.g. a loss of translational repressors such as FMRP, leads to fragile X syndrome (FXS). To investigate the role of FMRP in synaptic remodeling, we examined developmental profiles at the calyx of Held synapse in the auditory brainstem by measuring synaptic responses from prehearing immature (P6-9) and mature (P16-19) synapses in WT and FMRP KO mice. Our results indicated that loss of FMRP leads to accelerated subunit switching from slow gating GluA1-dominant to fast gating GluA4-dominant AMPARs, as evidenced

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by the increase in relative weight of mEPSCs with faster decay kinetics. In contrast, the developmental downregulation of NMDARs is stunted in FMRP KO synapses. Furthermore, NMDARs are also resistant to downregulation induced by coincident activation of Group1 mGluRs and NMDARs with patterned stimuli or agonists in FMRP KO synapses. The defective downregulation of NMDARs in FMRP KO synapses is acutely rescued by intracellular delivery of the N-terminus fragment of FMRP during whole-cell recordings, suggesting an non-canonical role of FMRP in modulating NMDAR plasticity. We propose FMRP can function as a canonical translational repressor to regulate AMPAR subunit switching, as well as a non-canonical signaling molecule to promote activity-dependent endocytosis of NMDARs which may underlie the synaptic, sensory, and cognitive deficits in FXS and autism.

3-B-39 *Δ9-THC regulates MANF expression, but not cellular restoration through the CB1R*

William McIntyre[1], Judith Tran[1], Ram Mishra[1]

[1]McMaster University

Background: Δ9-THC, the main psychoactive component of marijuana interacts with the most abundant receptor in the basal ganglia, the Cannabinoid Receptor 1 (CB1R). This ligand/receptor association has exhibited efficacy in the treatment of neurodegeneration. Dopaminergic cell death is characteristic of Parkinson's disease, which occurs through Endoplasmic Reticulum (ER) stress activation. Mesencephalic Astrocyte Neurotrophic Factor (MANF) regulates ER stress, but there is currently no evidence to support the relationship between the potential CB1R/MANF axis. Hypothesis: CB1R activation via Δ9-THC will induce Manf expression, which can be reduced through antagonizing the CB1R pathway. Increased cell viability will reflect identical treatments that induce Manf expression. Methods: This study was modelled in murine primary midbrain/immortalized striatal neurons. MTT assays and RT-qPCRs were used to quantify cell viability and gene expression, respectively. Results: Δ9-THC induces Manf in primary and immortalized neurons (p-values:0.0003,<0.0001 respectively), which can be abolished by CB1R antagonism (p-value<0.0001). Δ9-THC treatment can restore, and to a lesser extent protect neurons against 6-OHDA induced cell death (p-value:0.0288;0.0583, respectively), independent of the CB1R. Conclusions: This study suggests that Δ9-THC can regulate Manf expression through the CB1R, a protein that has been implicated in the treatment of basal ganglia related neurodegeneration. Despite this, restorative mechanisms likely occur independently of the CB1R.

3-B-40 *GluN1 N1-cassette regulates glycine-primed internalization and NMDA channel activity in hippocampal CA1 pyramidal neurons*

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Vishaal Rajani[1], Hongbin Li[1], Ameet Sengar[1], Danielle Chung[2], Lu Han[1], James Cooke[1], Michael Salter[1]

[1]The Hospital for Sick Children, [2]University of Toronto

N-methyl-D-aspartate receptors (NMDARs) are tetrameric ionotropic glutamate receptors that are composed of two GluN1 subunits and two of four possible GluN2 subunits. NMDARs are activated upon binding of co-agonists glycine and glutamate to the GluN1 and GluN2 subunits, respectively. We reported that glycine (30μM-1mM) initiates a signaling event that primes the receptors for dynamin-dependent endocytosis upon addition of glutamate (Nature 2003). Here we show that glycine-primed internalization of recombinant NMDARs expressed in HEK293 cells is prevented by the presence of alternatively spliced exon 5, encoding the N1-cassette of GluN1. Glycine stimulation induced a significant, progressive, ~50% reduction in NMDAR-mediated current in HEK293 cells expressing exon 5-lacking (GluN1a) subunits but not exon 5-containing (GluN1b) subunits. In hippocampal slices from genetically-modified mice expressing only GluN1a subunits, pretreatment with high glycine produced sustained decline in NMDAR-mediated synaptic currents (68.1±5.2% of baseline, n=13, $p<0.05$). By contrast, in slices from GluN1b mice, NMDAR-mediated synaptic currents showed no sustained decline (95.0 ± 6.5%, n=7, p=0.22). Our findings suggest that synaptic GluN1a-NMDARs, but not GluN1b-NMDARs, of hippocampal pyramidal neurons may be primed for internalization by glycine, leading to the depression of NMDAR synaptic transmission.

3-B-41 *A novel negative allosteric modulator (NAM) of the cannabinoid receptor 1 (CB1) as a potential therapeutic ligand for the treatment of psychiatric disorders arising from dopamine dysregulation*

Vincent Lam[1], Gemma Baillie[2], Iain Greig[3], Mostafa Abdelrahman[3], Laurent Trembleau[3], Ruth Ross[1]

[1]University of Toronto, [2]University of Dundee, [3]University of Aberdeen

The cannabinoid receptor 1 (CB1) receptor is a G-protein coupled receptor that is ubiquitously expressed in the brain. It has been shown that CB1 receptor antagonists have antipsychotic like effects in animal models of schizophrenia. Unfortunately, the side of effects of a CB1 antagonist in clinical trials led to the withdrawal of the drug from human use. With the discovery of an allosteric binding site on the CB1 receptor it is possible that allosteric modulators of the CB1 receptor may offer a unique and novel approach to rebalance the dopaminergic system at multiple points. By targeting the allosteric site of the CB1 receptor, we generated a novel negative allosteric modulator: ABM300. In cells stably expressing the CB1 receptor, we assayed ABM300 in several orthogonal assays quantifying arrestin recruitment, cAMP, and ERK phosphorylation. We tested the ability for ABM300 to allosterically modulate signalling of synthetic cannabinoids. Initial assays

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using arrestin recruitment, ABM300 showed negative allosteric modulation of the agonist CP55940. Further assays for quantifying cAMP signalling and ERK phosphorylation, also found that ABM300 acts as a negative allosteric modulator. In addition, in vitro pharmacokinetic analysis indicated that ABM300 has good in vivo drug stability and could have penetrance into the central nervous system. In conclusion, we show that ABM300 is a novel negative allosteric modulator for the CB1 receptor. Based on its chemical properties, we expect ABM300 to be active in the central nervous system for further in vivo characterization.

3-B-42 *NMDA receptor activation strengthens GABAergic signaling through a reactive oxygen species pathway*

Erik Larson[1], Michael Accardi[1], Martina D'Antoni[1], Derek Bowie[1]

[1]McGill University

Activation of NMDA-type ionotropic glutamate receptors (NMDARs) has been shown to increase cytosolic reactive oxygen species (ROS). While recent research has shown that cerebellar stellate cells are prone to ROS-mediated GABAergic strengthening (Accardi et all 2014 Nat Comm), NMDAR driven changes have not been previously investigated. In this study we set out to further examine activity driven plasticity of GABAergic synapses through NMDARs. By using whole-cell patch clamp electrophysiology our research demonstrates that NMDAR activation results in ROS mediated strengthening of GABAergic synapses. Furthermore we show that coupling between excitatory and inhibitory neurotransmission requires the activation of NOX2, nNOS, and PKC. We go on to reveal that this results in inhibitory synapse strengthening by recruitment of GABAR α3 containing receptors, not GABAR α1 receptors which are typically found in mature synapses of these neurons. Together, these findings reveal a novel regulation of GABA signaling which is mediated by prolonged activation of excitatory afferents.

3-B-43 *Bringing CLARITY to injury-induced astroglial plasticity within the sensorimotor cortex: effects of dental pulpectomy versus tooth extraction*

Jacqueline Lopez Gross[1], Ryuta Akasaka[1], Maryam Zanjir[1], Caitlin Sherry[1], Imran Alidina[1], Bettina Basrani[1], Pavel Cherkas[1], Limor Avivi-Arber[1]

[1]University of Toronto

Objective: To utilise the novel CLARITY technique to render the rat sensorimotor cortex (SM) optically transparent, and use immunolabelling to quantify morphological features of astroglia in the primary motor (M1) and somatosensory (S1) cortex, and test if endodontic treatment vs tooth extraction induces differential changes in astroglial morphology. Methods: Under general and

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local anaesthesia, male Sprague-Dawley rats (175-200g; n=5/group) received pulpectomy or extraction of 3 right maxillary molar teeth. Sham rats received anaesthesia and mouth opening but no actual treatment. Naive rats received no treatment. Rats were perfused on postop day 7. Brains were passively cleared. SM coronal sections (2 mm) were immunolabelled with GFAP, a specific astroglial marker. 3D-Z-stack images (0.2 x 0.5 x 1 mm3) of S1/M1 layers 1-2 were acquired with Zeiss Lightsheet microscope (x20). Imaris software automatically quantified volume, surface area, diameter, and straightness of astroglial filaments. Statistics used ANOVA and post-hoc tests ($p < 0.05$). Results: Significant differences in the morphological features of astroglial filaments were observed between S1 and M1, layer 1 and 2 and in the effects of pulpectomy vs tooth extraction. Conclusion: Along with our previously published electrophysiological studies (Avivi-Arber et al, Awamleh et al, 2015), astroglia are involved and may play critical roles in SM neuroplasticity induced by dental injury, and may be a potential therapeutic target to treat or prevent sensorimotor impairment induced by dental injury.

3-B-44 *Microglia prevents white matter maturation delay induced by systemic inflammation in the developing cerebellum*

Sophie Tremblay[1], Alex Pai[1], Laurine Legroux[2], Dan Goldowitz[1]

[1]Centre for Molecular Medicine and Therapeutics, [2]CHU Sainte-Justine Research Center/Université de Montréal

Extreme preterm infants are exposed to multiple inflammatory stressors over their neonatal period including perinatal cerebellar hemorrhage (CBH) and postnatal infection. By using a transgenic mouse model allowing microglia depletion prior to cerebellar insult, the pathophysiological impact of microglial cells on the developing cerebellum will be studied. Conditional transgenic mice dependent on diphtheria toxin intracerebellar injection to deplete CX3CR1-positive cells were made and CBH was induced at P2 combined with early inflammation (EIS). Microglial cells depletion at P2 prior to insult reached a residual level of 27.9±7.7% in caudal brain regions (***P = 0.0003). Rostral brain regions were also affected to a lesser extent (35.6±10.3%, ***P = 0.0062). Measurement of sensorimotor reflexes over the neonatal period reveals a significant delay of grasping acquisition in CX3CR1-depleted pups exposed to EIS (*P = 0.03) or CX3CR1-depleted pups exposed to vehicle (**P = 0.0053). Microglia-depleted mice exposed to early inflammation tend to have smaller cerebellum (P = 0.0517) and reduced total cerebellar white matter (WM) volume (P = 0.0717). Expression of O4 oligodendrocyte maturation marker is significantly reduced at P15 in cerebellar WM exposed to early inflammation of microglia-depleted mice (*P = 0.0401). Microglia-depleted mice exposed to early inflammation have altered sensorimotor reflexes acquisition and delayed cerebellar WM maturation compared to non-depleted mice implying a protective role for microglial cells after EIS insult on cerebellar WM tissue.

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3-B-45 *GluN2 heterogeneity across individual primary afferent-lamina I neuron synapses differentially encodes sensory input in the adult rat lumbar spinal cord*

Graham Pitcher[1], Livia Garzia[2], Michael Taylor[1], Michael Salter[3]

[1]SickKids Research Institute, [2]McGill University, [3]The Hospital for Sick Children

The vertebrate spinal dorsal horn is a major CNS region where somatosensory information is processed before relay to the brain. Lamina I dorsal horn neurons are critical in this function as their dendrites are the primary target of synaptic contacts from peripheral nociceptors, the majority of which are glutamatergic. Because GluN2 subtypes of the NMDA glutamate receptor class exhibit distinct properties and downstream functions, a major question is GluN2 subunit composition at individual primary afferent-lamina I neuron synapses. To elucidate synaptic subtype, we recorded from lamina I neurons in acute spinal slices from rats and evoked unitary excitatory postsynaptic currents (uEPSCs; Vh +60mV) by stimulating single afferent monosynaptic connections (n=224). Cluster analysis of uEPSC decay constant and charge transfer identified 3 groups showing that uEPSCs derive from NMDARs with distinct kinetic properties. In one group (36%) uEPSC decay was fast (52ms) and charge transfer small; a second subpopulation (13% only) had a long decay (1219ms) and large charge transfer while 51% of synapses had an intermediate decay (315ms) and charge transfer. GluN2B block reduced intermediate uEPSCs while GluN2D block reduced slow uEPSCs and GluN2A block reduced fast uEPSCs. Thus, unitary lamina I glutamatergic synaptic responses are not identical but occur with distinct properties consistent with those of GluN2A, 2B, or 2D NMDARs. The more abundant GluN2A-2B suggests a synaptic subunit composition favoring fast-intermediate NMDAR kinetics in detecting and integrating sensory input.

3-B-46 *Response properties from theta-burst stimulation of limbic structures in humans*

Chaim Katz[1], Kramay Patel[1], Taufik Valiante[2]

[1]University of Toronto, [2]Krembil research Institute, University Health Network

Background: How strongly two regions of the brain interact with one another is often estimated as "functional connectivity". Electrical stimulation offers one approach to estimate functional connectivity from the amplitude of corticocortical evoked potentials (CCEP). Typically, CCEPs are evoked using single pulse stimulation. However, previous in-vitro and in-vivo animal work has shown that the parameters of stimulation such as theta burst stimulation has demonstrated long term potentiation and enhanced memory. Methods: CCEP functional connectivity was assessed between limbic structures and other subcortical and cortical sites using theta-burst stimulation pattern (a burst of five biphasic pulses at 500Hz, repeated three times a second, 0.1ms pulse width). Intensity was increased from the initial level of 0.5mA until a significant response was

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recorded in any grey matter location. The amplitudes were compared to those found from connectivity results from other stimulation studies. Results: Our preliminary results suggest that CCEP amplitudes may be different when using theta burst stimulation versus single pulse stimulation. For instance, increasing amplitude of the response did not necessarily result in increased CCEP amplitudes in stark contrast with CCEPs elicited with single pulse stimulation. Conclusion: Future work will focus on performing such connectivity studies using both theta-burst and single-pulse stimulation to elicit within-subject differences and explore potential mechanisms to explain any observed differences.

3-B-47 *Alternative splicing of exon 5 in GluN1 controls glycine-stimulated recruitment of AP-2 to NMDA receptors*

Danielle Chung[1], Ameet Sengar[2], Michael Salter[2]

[1]University of Toronto, [2]The Hospital for Sick Children

N-methyl-D-aspartate receptors (NMDARs) are important for synaptic plasticity and memory and learning. NMDARs are heterotetramers that require binding of both agonists, glycine and glutamate, to their respective GluN1 and GluN2 subunits, for channel activation. We have shown that high glycine triggers an increased association of the endocytic adapter protein complex AP-2 with NMDARs, priming them for endocytosis upon glutamate activation (Nong et al., Nature 2003). Here we discovered that priming of NMDARs is dependent on the state of splicing of exon 5, which encodes a 21 amino acid cassette (N1-cassette) in the extracellular amino terminal domain of the GluN1 subunit. Using acute hippocampal slices from genetically modified mice lacking exon 5 (GluN1a) or compulsorily expressing exon 5 (GluN1b), we found a robust increase in AP-2/NMDAR association in GluN1a (268±48% of control, p=0.02) versus GluN1b mice (115±11% of control, n.s.) after 1mM glycine stimulation for 10 minutes. We found high glycine stimulation resulted in significant dephosphorylation at GluN1-S896 (70.49±8.6% of control, p=0.02) and GluN2B-S1480 (81.8±4.4% of control, p=0.01) in GluN1a but not in GluN1b slices. Moreover, basal phosphorylation of GluN1-S896 and GluN2B-S1480 were significantly higher in GluN1a slices compared to GluN1b. Our findings suggest that splicing out exon 5 of GluN1 yields NMDARs that are differently dephosphorylated in response to high glycine allowing AP-2 to bind the receptors. Thus, differential splicing of exon 5 may selectively control stability of cell-surface NMDARs.

3-B-48 *Pannexin 1 regulates network ensembles and dendritic spine development in cortical neurons*

Juan Sanchez-Arias[1], Mei Liu[2], Catherine Choi[1], Sarah Ebert[1], Ana De Lucas-Rius[1], Craig Brown[1], Leigh Anne Swayne[1]

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[1]University of Victoria, [2]Nantong University

The brain functions as interconnected networks of neurons. These connections are formed as neurons develop microscopic processes that enable communication at highly specialized structures called synapses. Based on our discovery that the Pannexin 1 (Panx1) channel protein regulates neurite growth, we investigated the hypothesis that Panx1 regulates the formation of neuronal networks. Network analysis from Ca2+ transients in cortical neuron cultures from WT and Panx1 KO mice revealed more (and larger) neuronal networks in Panx1 KO cultures. To better understand the basis for this increased in neuronal networks, we examined structural connectivity. Excitatory inputs converge into specialized microscopic protrusions called dendritic spines, that grow from dendritic shafts. We reasoned an increase in dendritic spines could account for the larger number and size of neuronal networks. To measure dendritic spine density, we labeled WT and Panx1 KO somatosensory layer 5 cortical neurons ex vivo with a lipophilic fluorescent dye, DiI, at P14 and P29, a critical period for dendritic spine formation. At both ages, Panx1 KO neurons showed increased spine density. We made similar observations in a glutamatergic-specific Panx1 KO as well as in cultured cortical neurons, demonstrating the effect is cell autonomous. Accordingly, analysis of protein expression in cortical synaptosomes revealed increases in PSD-95, GluA1, and GluN2A. Taken together, these data reveal a new role for Panx1 in the formation of cortical neuronal networks through regulating the development of dendritic spines.

3-B-49 *Decreases in cellular firing dominate within the perisacaddic interval in human mesial temporal lobe structures and occipital lobe*

Andrea Schjetnan[1], Chaim Katz[2], Kramay Patel[2], Victoria Barkley[1], Taufik Valiante[3]

[1]Toronto Western Hospital, UHN, [2]University of Toronto, [3]Krembil research Institute, University Health Network

Background: In the primate brain, saccadic eye movements are strongly correlated to mnemonic processing. Invasive local field potential (LFP) recordings in humans have shown saccade associated potentials in mesial temporal lobe (MTL) structures that demonstrate phase clustering in the theta and alpha bands without associated power increases. This specific electrophysiological signature suggests that neuronal excitability is not increased following saccadic eye movements Methods: To explore this hypothesis we performed single unit recordings in epilepsy patients undergoing electrophysiological evaluation. The location of the clinical macro-electrodes was determined clinically. Subjects performed a visual search task, with continuous eye tracking to ascertain saccade onset timing. Offline spike sorting followed by peri-saccadic time histograms were constructed for well separated units. Results: Our preliminary analyses reveal that neurons in the MTL and occipital lobe are modulated by saccade onset. Conspicuously a peri-saccadic decrease in the firing rate was observed in the majority of units from occipital sites, and approximately 20% of units found in MTL structures. Occipital units

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additionally demonstrate a 'rebound' increase in spiking following the inhibitory period, whereas the MTL units did not. Conclusions: Single unit recordings in humans suggest that inhibition likely dominates the peri-saccadic interval in MTL structures and neocortical regions. These results are consistent with the lack of power increases observed in the LFP in MTL sites.

3-B-50 *Stress modulates the plasticity of glutamate synapses in the dorsomedial hypothalamus in rats*

Karen Crosby[1], Tenea Welsh[1]

[1]Mount Allison University

The dorsomedial hypothalamus (DMH), a major appetite-regulatory center, is in an ideal position to respond to stress and potentially mediate stress-induced changes in food intake. DMH neurons express glucocorticoid receptors and receive extensive input from the paraventricular nucleus. Stress affects the plasticity of GABA synapses in the DMH, but it remains unknown whether stress modulates glutamate synapses. Thus, the objective of this study was to examine the effect of stress on glutamate synapses in the DMH. Young, male Sprague Dawley rats were placed in one of the following groups: a) naïve (no stress), b) acute restraint stress (30 min), c) repeated restraint stress (30 min/day for 5 days), or d) 24 hours of food deprivation, the latter of which triggers stress-induced alterations in DMH GABA synapses. Animals were then anesthetized and brains sliced for whole cell electrophysiological recordings. Excitatory postsynaptic currents were evoked and the effect of stress on the plasticity of glutamate synapses following high frequency stimulation (HFS) was examined. We show that glutamate synapses undergo short-term potentiation following HFS but fail to exhibit long lasting changes in synaptic strength. Following acute or repeated restraint stress, these synapses exhibit long-term depression following HFS. In contrast, food deprivation elicits long-term potentiation of glutamate synapses. Overall, we demonstrate that stress impacts the plasticity of glutamate synapses in the DMH. This research could provide insight into how stress acts in the brain to influence appetite.

3-B-51 *A recurrent network motif in the dorsal raphe nucleus supports an operational classification of habenula inputs*

Michael Lynn[1], Sean Geddes[1], Mohamad Chahrour[1], Sebastien Maillé[1], Emerson Harkin[1], Samir Haj-Dahmane[2], Richard Naud[1], Jean-Claude Beique[1]

[1]University of Ottawa, [2]University at Buffalo, State University of New York

The habenulo-raphe pathway is believed to be implicated in orchestrating optimal behavioral responses to aversive, threatening or stressful environments. Here, we consider how long-range

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inputs from lateral habenula (LHb) influence circuit dynamics in the dorsal raphe nucleus (DRN) using optogenetic strategies, whole-cell electrophysiology, computational modeling and behavior. High-frequency (20Hz), but not lower-frequency optogenetic activation of LHb axons triggered a novel form of protracted feed-forward inhibitory processing in the DRN network, occurring in parallel with classical monosynaptic excitatory and disynaptic inhibitory conductances. The induction of this protracted LHb-driven, seconds-long hyperpolarizing response was mediated by a GIRK conductance activated by 5-HT1ARs. Optogenetic manipulations in the DRN suggest that this protracted inhibition is mediated not by a cell-autonomous autoinhibition mechanism, but rather by a feedforward inhibition enacted by 5-HT neurons organized in an unsuspected recurrent network architecture and bearing features of a synaptic accumulator. We also constructed a minimal, biophysically plausible network model which replicates key features of our findings. Notably, this network architecture enacts a dynamically-regulated low-pass filter that is suited to classify a linearly represented environmental feature (e.g. increasing threat level) to support the emergence of a binary behavioural outcome (e.g. go/no-go) - a capability that is perhaps generalizable to other hub-like networks in the brain.

3-B-52 *Spinal DNA methylome and transcriptome signature after peripheral nerve injury (PNI)*

Shahrzad Ghazisaeidi[1], Parisa Shooshtari[2], Arun Ramani[2], Amy Tu[2], Katherine Halievski[2], David Finn[3], Sofia Assi[1], Milind Muley[2], Vivian Wang[2], Ameet Sengar[2], Rosanna Weksberg[2], Michael Brudno[2], Michael Salter[2]

[1]University of Toronto, [2]The Hospital for Sick Children, [3]National University of Ireland

Chronic pain affects 1 in 5 Canadians and costs over $43B annually, yet effective and safe treatment options remain elusive. Recent discoveries have brought to the forefront sex differences in mechanisms of pain as a potential explanation why novel pre-clinical therapeutics have not translated into successfully in clinical trials. To begin understanding how males and females differ in pain processing, we analyzed gene expression, using RNA sequencing, and DNA methylation, using reduced representation bisulfite sequencing (RRBS), in rodent models of neuropathic pain. Across both sexes, our data reveals peripheral nerve injury (PNI) caused upregulation of 61 genes involved in innate immune responses in spinal cord. In females specifically, we observed PNI-induced downregulation of 5 genes involved in neuronal function and upregulation of two classes of cathepsins (C & E). Whereas, in males, we observed upregulation of 14 genes including those involved in metabolism of purines. Additionally we found that PNI leads to methylome remodeling in a sexually dimorphic manner. We found 125 promoters in rat spinal cord that were differentially methylated in PNI males versus females. We observed a robust sex specific DNA methylation and transcriptome signature after PNI. Our data leads to the hypothesis that remapping of DNA methylation, with subsequent alterations in the transcriptome, are critically involved in the

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development of neuropathic pain.We anticipate that future research directed at understanding these differences may lead to effective drug development to combat chronic pain

3-B-54 *Impact of optogenetic perturbation of phospholipids on release and replenishment of synaptic vesicles in central nerve terminals*

Shuwen Chang[1], Lu-Yang Wang[1]

[1]The Hospital for Sick Children

Phosphatidylinositol 4,5-bisphosphate (PIP2) is a phospholipid that plays key roles in many cellular signaling. Its unique property of carrying multiple negative charges enables PIP2 to recruit downstream effector proteins in a spatiotemporal manner. However, directly studying its role has been technically challenging due to the lack of temporal control or spatial resolution that allows subcellular manipulation. Here, we employed an optogenetic tool that enables transient and reversible manipulation of subcellular phosphoinositide within seconds in mammalian central nervous synapses. In combination with electrophysiology and optical images, we investigate the functional role of phosphoinositide in regulating the kinetics of synaptic vesicle (SV) release and replenishment. Our preliminary data showed that the recovery of readily releasable SV was delayed upon light-induced PIP2 depletion. Specifically, PIP2 depletion only affected fast recovery (Ca2 -dependent replenishments). Our optogenetic tool allows direct access for functional analyses of PIP2 in synaptic loci, and more importantly to gain insights into the intricate lipid metabolism and signaling to modulate protein-protein interactions for fusion at the active zone of central nerve terminals.

3-B-55 *Pannexin1 channels and dopamine receptor signaling; old players and new prospects*

Nickie Safarian[1], Paige Whyte-Fagundes[1], Christiane Zoidl[1], Joerg Grigull[1], Georg Zoidl[1]

[1]York University

A novel mechanism was discovered affecting dopaminergic (DA) transmission and DA receptors in a pannexin-1 (Panx1) knockout zebrafish model. Panx1 proteins form unopposed plasma membrane channels with complex gating characteristics. Aiming at a comprehensive perspective on Panx1 functions, we generated a zebrafish knock out model using TALEN technology. RNAseq demonstrated that loss of panx1 had a distinct impact; 931 mRNAs were upregulated and mainly involved in photo-transduction, as well as in the development of the visual system. 1901 mRNAs were downregulated and largely overlapped with the cells transportome, which collectively refers to ion channels, purinergic and neurotransmitter receptors, solute carrier (SLC) transporters and

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other related categories of proteins providing a fundamental membranal/motile scaffold involved in the development and physiology of the nervous system. Altered visual motor activity of panx1-/- larvae and in vivo electrophysiological recordings were consistent with transcriptome changes confirmed by qPCR. Larvae exhibit a disruption of the dopamine (DA) signaling pathway involving the pre-synaptic dopamine synthesis and release processes and post-synaptic dopamine signaling through D2R-like pathways. Pharmacological intervention with dopamine receptors and rescue by D2R agonist treatment mimicked the phenotype. The association between Panx1 and dopaminergic signaling will provide an opportunity to study the roles of Panx1 in regulating synaptic transmission through dopamine in an animal model suitable for high-content analysis.

3-B-56 *Frequency-dependent coupling between neuronal activity and mitochondrial Ca2+ dynamics in situ*

Chris Groten[1], Brian MacVicar[1]

[1]University of British Columbia

Information processing by the brain is critically dependent on mitochondrial ATP production. Consequently, disrupted mitochondrial function can have dramatic consequences for brain health. Considering this, it is essential to directly visualize and study mitochondrial properties in the intact nervous system. A well-known property of mitochondria is Ca2+ handling, which has been linked to ATP/ROS production, apoptosis, and cytosolic Ca2+ signalling. Despite this, the relevance of this process to the function of the mammalian brain is unclear. To address this, I utilized two-photon microscopy to directly examine mitochondrial Ca2+ in pyramidal neurons from rodent brain slices. Whole-cell recordings from neurons expressing the mitochondrial Ca2+ reporter, mitoRGECO1.0, revealed a threshold of action potential firing frequency (5 Hz) above which there was a prolonged increase in mitochondrial Ca2+. These responses were occluded by preventing plasma membrane Ca2+ entry or inhibiting the mitochondrial Ca2+ uniporter (MCU)- a Ca2+ channel- with Ru360. Ru360 also enhanced the magnitude/duration of cytosolic Ca2+ at action potential frequencies greater than 5 Hz. Moreover, blocking the MCU shaped activity-dependent membrane currents and disrupted cellular energy homeostasis. Collectively, our results reveal that increases in mitochondrial Ca2+ are mediated by the MCU in pyramidal neurons. Moreover, we identified the MCU as a key regulator of pyramidal neuron function during periods of heightened activity due to its influence on membrane excitability and energy homeostasis.

3-B-57 *Enhanced LTP in mice lacking the endogenous cellular prion protein*

Aeen Ebrahim Amini[1], John Georgiou[2], Changiz Taghibiglou[3], Graham Collingridge[1]

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[1]University of Toronto, [2]Lunenfeld-Tanenbaum Research Institute, Mt. Sinai Hospital, [3]University of Saskatchewan

In the brain, AMPA receptors (AMPARs) are the major glutamate receptors that are involved in neuronal communication. Increases and decreases in AMPAR number, composition, distribution, and efficacy represent some of the mechanisms that neurons employ to modulate their communication strength; such changes occur at synapses. This process, known as synaptic plasticity, represents the critical underlying mechanism that the brain employs when performing cognitive functions such as learning and memory. Defects in synaptic plasticity are responsible for many brain disorders such as Alzheimer's Disease (AD). Previous studies have shown that cellular prion protein (PrPC) interacts with AMPARs, and thus could play a role in synaptic function; however, its role has not been elucidated. We used electrophysiological techniques to explore the function of PrPC at Schaffer collateral-CA1 synapses in the hippocampus, a region critical for learning and memory, and preferentially affected in AD. We have found that C57BL/6J-Prnp knockout (KO) mice have normal long-term potentiation (LTP) when induced using a theta-burst stimulation protocol (75 pulses), but show enhanced LTP when evoked using a weak induction protocol (25 pulses). We further studied the mechanism underlying the enhanced LTP in KO mice using KT 5720, a selective inhibitor of protein kinase A (PKA). Preliminary data show that KT 5720 did not have any effect on wild type (WT) mice when triggered with the weak induction protocol but reduced LTP in KOs. These preliminary data suggest that the enhanced LTP in KOs is mediated by PKA, and therefore loss of PrPC dysregulates PKA. Ongoing investigation will further examine the underlying mechanism of enhanced LTP in KO mice.

3-B-58 *Ankyrin-B p.S646F increases the intracellular pool of Cav2.1*

Catherine Choi[1], Ivana Souza[2], Juan Sanchez-Arias[1], Gerald Zamponi[2], Laura Arbour[3], Leigh Anne Swayne[1]

[1]University of Victoria, [2]University of Calgary, [3]University of British Columbia

In neurons, the Ankyrin B (AnkB) scaffolding protein is detected in synaptic compartments, interacts with the pore-forming subunit of P/Q type voltage gated Ca2+ channels (Cav2.1) and is associated with neurodevelopmental disorders like Epilepsy. We recently discovered a novel AnkB p.S646F variant associated with several cardiac phenotypes as well as seizure in the Gitxsan First Nation of Northern British Columbia. Here, we investigated the impact of AnkB p.S646F or partial loss of AnkB expression on Cav2.1 expression and trafficking. Co-expression of AnkB p.S646F in HEK293 cells increased whole cell Cav2.1 expression, with no change in cell surface levels or AnkB-Cav2.1 binding affinity. Whole cell patch clamp demonstrated that AnkB p.S646F did not significantly increase Cav2.1 current amplitude, consistent with a lack of effect on Cav2.1 surface levels. Consistent with the role of AnkB in regulating whole cell (or intracellular) Cav2.1 levels, a significant reduction of Cav2.1 levels was observed in whole cortex lysates, but not in

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cortical synaptosomes from glutamatergic neuron-specific AnkB KO mice. These results suggest AnkB does not facilitate surface or synaptic Cav2.1 localization, but rather regulates an intracellular pool of Cav2.1, and that this intracellular pool is increased with expression of the AnkB p.S646F variant. Precisely how the increase in intracellular Cav2.1 levels could lead to increased seizure incidence (e.g. activity-dependent cell surface recruitment) remains to be fully elucidated.

3-B-59 *A role for glycogen synthase kinase-3β as a regulator of prefrontal cortical and hippocampal neuronal oscillations in cognition*

Abdalla Albeely[1], Melissa Perreault[1]

[1]University of guelph

Glycogen Synthase Kinase-3beta (GSK-3β) is a constitutively active serine/threonine kinase that has been implicated in the pathology of several neuropsychiatric disorders characterized by cognitive dysfunction including schizophrenia. These disorders also exhibit dysregulation in neuronal oscillatory activity, which is known to contribute to cognitive decline. Specifically, neuronal oscillations play a key role in the synchronization of neuronal activity within and between brain regions, a process critical to brain functions such as learning, memory formation, and behaviour. A link between GSK-3β activity and neuronal oscillatory activity has not been established. In this research, we investigated a role for GSK-3β in the regulation of neuronal oscillations in the prefrontal cortex (PFC) and hippocampus (HIP), two regions integral to learning and memory processes. The study employed an AAV construct with a human mutant GSK-3β(S9A) that was persistently active. The AAV- GSK-3β(S9A) was injected bilaterally into PFC or HIP and the effects on neuronal oscillatory activity and cognition evaluated. Preliminary data showed that increased GSK-3β in the HIP but not the PFC impaired spatial memory and reversal learning. Local field potential recording analysis showed that increased activation of GSK-3β in the HIP increased the overall total spectral power in the PFC region indictive of hypersynchronous neuronal activity in that region. These preliminary results are the first to directly link GSK-3β activity in HIP to the modulation of neuronal oscillations in the PFC, thus identifying an underlying mechanism by which GSK-3β regulates cognitive function.

C - Disorders of the nervous system

3-C-60 *Synaptic Modifications Induced by Starvation at Drosophila Neuromuscular Junctions (NMJ)*

Gretchen Macias-Mendez[1], Ramon Jorquera[1]

[1]Universidad Central del Caribe

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Neuronal transmission is highly plastic and undergoes short-term changes during and after high-frequency nerve-activity episodes. Short-term synaptic-memory is observed in most chemical synapses, being energetically demanding and a basic process in the animal kingdom. As commonly known, starvation can produce significant changes like behavior, memory, and synaptic computation impairments which have been attributed to cellular energy states. At cellular levels, starvation increases autophagy by the inhibition of mTor to prevent protein translation and activates the lysosome for energy production. However, if and how those targets modify the short-term synaptic-memory remains unknown. Therefore, we scrutinized the effect of acute fasting in the synaptic behavior using the Drosophila NMJ as model. Control strains after starving displayed nerve-evoked hyperexcitability and progressive nerve fatigue. Those conditions are prevented in animals grown in supplemented food. Those synapses exhibit impaired short-term synaptic-memory in two quantal release probabilities. At rest, asynchronous neurotransmission is dramatically increased. Our work suggests that starvation induces short-term synaptic memory loss. Our observations are consistent with energy reduction after starvation impacting the efficiency of nerve-terminals to control resting membrane potential and synaptic vesicle trafficking. As autophagy is directly connected with membrane recycling via the endo/lysosomal system, vesicle trafficking and reformation slowdown or impairment may account for this memory deficit as well.

3-C-61 *Mitochondrial function and antioxidant mechanisms of astrocytes in fragile X syndrome*

Gregory Vandenberg[1], Alison Head[1], Neal Dawson[1], Angela Scott[1]

[1]McMaster University

Fragile X Syndrome (FXS), a genetically-linked neurodevelopmental disorder, is associated with alterations in the formation and function of neural circuitry, learning deficits, anxiety and seizures. Due to this, changes in reactive oxygen species (ROS) production, lipid peroxidation, and protein oxidation within cortical regions may be associated with this disorder. Any potential imbalances to these or antioxidant systems can lead to oxidative stress. Astrocytes, glial cells within the brain, have many functions within neurodevelopment. Specifically, they regulate growth and synaptic contacts of neurons, regulate the level of excitability of synapses, and are the primary providers of antioxidants within the CNS. This study examines the potential relationship between oxidative stress and FXS by assessing mitochondrial function and corresponding antioxidant supply via astrocytes. Using an animal model of FXS, the fmr1 knockout (KO) mouse model, mitochondrial respiration and ROS production in cultured cortical astrocytes were analyzed. In addition, protein expression and enzyme activity were measured to determine potential differences in antioxidant production or metabolism in KO versus wild-type (WT) astrocytes. Preliminary results indicate genotypic differences in ROS production, glutathione peroxidase expression, and glutathione-

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protein complex expression in cortical astrocytes. Future steps involve assessing mitochondrial function and antioxidative systems of astrocytes in vivo and within physiological hypoxia to further evaluate oxidative conditions in FXS.

3-C-62 *Chemotherapeutic ablation of seizure-induced neurogenesis attenuates cognitive impairments after long-term amygdala kindling*

Travis Francis[1], Brady Reive[1], Hugo Lehmann[1], Neil Fournier[1]

[1]Trent University

Repeated seizure stimulation robustly stimulates neurogenesis. However, many newborn neurons generated after seizures appear to integrate abnormally and are hyperexcitable. We have previously shown that amygdala kindling dramatically increases the rate of neurogenesis at early stages of seizure development, followed by a long-term suppression at later stages. These changes in the rate of cell proliferation coincide with aberrant modifications in the migration, excitability, and functional integration of these new neurons. The abnormal integration of newborn neurons following seizures is thought to disrupt hippocampal circuits and contribute to cognitive impairments. However, direct experimental evidence has been limited. To explore this question, we inhibited neurogenesis by administering the DNA-alkylating agent temozolomide (TMZ) in male Long-Evans rats that underwent long-term amygdala kindling. Kindled rats began treatment with TMZ (50 mg/kg, i.p.) after their 30th stimulation and kindling proceed until 75 stimulations were delivered. We found that TMZ reversed seizure-induced deficits in contextual fear learning and context discrimination. We plan to expand our studies to also examine whether blocking seizure-induced neurogenesis reduces anxiety and depressive-like behaviours. These preliminary findings support the idea that suppressing seizure-induced neurogenesis can improve memory impairments, and helps to further establish that targeting aberrant neurogenesis can serve as a novel approach for reducing cognitive deficits associated with epilepsy.

3-C-63 *Dickkopf-related protein 1 (DKK1) inhibition attenuates Amyloid-beta (Aβ)-related pathology in APP/PS1 mice*

Romain Menet[1], Maxime Bernard[1], Sarah Lecordier[1], Philippe Bourassa[1], Frédéric Calon[1], Ayman ElAli[1]

[1]Université Laval

DKK1 inhibits the canonical Wnt pathway by preventing Wnt ligands from binding the receptor complex formed by Frizzled (Fzd) and low-density lipoprotein (LDL) receptor-related protein-5/6 (LRP5/6). Wnt ligands binding to Fzd/LRP5/6 stabilizes β-catenin in the cytosol and stimulates its

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subsequent translocation to the nucleus to regulate transcription of target genes implicated in a wide range of physiological processes in the brain. Canonical Wnt pathway deactivation is associated to the onset and progression of Alzheimer's disease (AD). Interestingly, DKK1 levels are elevated in the AD brain. Our study aimed to elucidate DKK1 role in AD pathology. For this purpose, aged APP/PS1 mice were repeatedly treated with a DKK1 inhibitor, WAY262611. β-catenin expression increased after WAY262611 administration, confirming canonical Wnt pathway activation. DKK1 inhibition decreased Aβ plaque number, reduced soluble Aβ1-42 level, and ameliorated cognitive functions of mice. Aβ pathology attenuation was accompanied by a reduced expression of beta-site APP cleaving enzyme 1 (BACE1), which is involved in Aβ production. DKK1 inhibition promoted blood-brain barrier (BBB) function, which contributes to Aβ clearance, by increasing expression of claudin 5, glucose transporter-1 (GLUT-1), and ATP-binding cassette sub-family B member 1 (ABCB1). Finally, DKK1 inhibition recovered expression of brain-derived neurotrophic factor (BDNF), which is involved in synaptic plasticity. Our results indicate that DKK1 inhibition constitutes an elegant approach to attenuate and reverse AD progression.

3-C-64 *Combined rapid amygdaloid kindling and corticosterone treatment induces anxious depression in rats*

Brady Reive[1], Travis Francis[1], Neil Fournier[1]

[1]Trent University

Anxiety and depression are the most frequent and disabling neuropsychiatric comorbidities associated with mesial temporal lobe epilepsy. The neurobiological mechanisms underlying the co-occurrence of these psychiatric conditions in epileptic patients remains poorly understood. In the present study we demonstrated that a combination of rapid amygdala kindling along with sub-optimal corticosterone treatment can produce robust changes in both anxiety and depressive-like behaviour in rodents. In our study rats underwent two cycles of rapid kindling (40 stimulations administered over two days, i.e. 20 stimulations per day) carried out 1-week apart for a total of 80 electrical stimulations per subject. During the 1-week period between kindling a subset of rats received corticosterone (40 mg/kg). We have previously shown 1-week treatment of corticosterone at this concentration does not induce changes in anxiety or depressive-like behaviour. Following kindling rats underwent behavioural tests selected to assess anhedonia, exploration, anxiety, and depressive behaviours. Rapid kindling alone produced a slight increase in hyperactivity during exposure to an unfamiliar environment, but combining kindling with corticosterone resulted in decreased sucrose consumption, altered immobility in the forced swim test, and increased behavioural hyperactivity. Our findings suggest that limbic seizures and elevated stress hormone can increase vulnerability to development of both anxious and

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depressive-like behaviours. Future research will explore molecular mechanisms underlying this relationship.

3-C-65 *Circadian regulation of the RNA binding protein FXR1*

Tiago Silva[1], Alesya Evstratova[1], Aleksandra Marakhovskaia[1], Valerie Mongrain[2], Jean-Martin Beaulieu[1]

[1]University of Toronto, [2]Université de Montréal

Fragile X Related Protein 1 (FXR1) is an RNA-binding protein that plays a role in the regulation of protein synthesis. Several studies have shown a link between FXR1 and Bipolar Disorder (BD). It is well known that BD patients suffer from sleep disturbances and circadian clock dysfunction. Our previous work shows that FXR1 responds to chronic lithium treatment by increasing its protein levels in the prefrontal cortex (PFC). The objective of this study is to assess if FXR1 is regulated in a circadian-dependent manner in the context of BD. Luciferase reporter assays with FXR1 mouse or human promoter were performed in COS-7 cells transfected with CLOCK, BMAL1 and NPAS2 (a CLOCK homolog). FXR1 mouse promoter luminescence counts were increased 1.5-fold in the presence of CLOCK and BMAL1 when compared to the control condition absent of the two clock genes.Moreover, BMAL1 and NPAS2 induced a close to 3-fold increase in luciferase counts from both mouse and human FXR1 promoters. To check for FXR1 regulation in vivo, we used a mouse model of BD (clock delta19, which presents disrupted circadian system), and dissected PFC and hippocampal samples at different time-points. qPCR analysis shows an ablation of FXR1 mRNA oscillations in clock delta19 when compared to wild-type littermates both in PFC and hippocampal samples. These results indicate that FXR1 is regulated at the transcription level by the circadian clock system and seem to support the potential involvement of FXR1 in BD. Thus, FXR1 might become an interesting target to study BD.

3-C-66 *FABP 5 gene ablation promotes resilience to stress reinstatement for cocaine seeking behavior in mice*

John Hamilton[1], Matthew Marion[1], Antonio Figueiredo[1], Eleftherios Hetelekides[1], Amanda Nubelo[1], Meagan Schreiner[1], Rylee Haffey[1], Nicole Roeder[1], Carly Connor[1], Panayotis Thanos[1]

[1]Jacobs School of Medicine, University at Buffalo

Fatty acid-binding proteins (FABPs) are intracellular carriers for endocannabinoids (like anandamide) and related N-acylethanolamines (palmitoylethanolamide and oleoylethanolamide). FABP subtype 5 are particularly abundant in the CNS and represent potential targets for manipulating endocannabinoid signaling. Mice lacking the genes for FABPs 5 have been shown

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to exhibit increases in AEA as well as PEA and OEA. Given the strong relationship between endocannabinoid signaling and reward, the goal of this study is to examine cocaine-seeking behavior in mice lacking the FABP5 gene. Cocaine-seeking behavior was assessed using the conditioned place preference (CPP) paradigm. Results show that FABP5 knockout (KO) mice display no changes in the acquisition for a cocaine CPP compared to wild-type (WT) mice, but fail to show a stress reinstatement. Moreover, mice lacking the FABP5 gene show reductions in corticosterone levels following restraint stress. Furthermore, female, but not male, FABP5 KO mice show a blunted locomotor response to cocaine. Lastly, male FABP5 KO mice show a delay in the extinction of a cocaine CPP. These results demonstrate the FABP5 gene plays an important role in stress-induced relapse to cocaine-seeking behavior, but may play different roles on reward-related learning.

3-C-67 *Using eye tracking to identify saccade biomarkers of neurodegenerative disease*

Heidi Riek[1], Brian Coe[1], Don Brien[1], Sandra Black[2], Michael Borrie[3], Dar Dowlatshahi[4], Elizabeth Finger[3], Morris Freedman[5], David Grimes[4], Donna Kwan[6], Anthony Lang[7], Connie Marras[7], Mario Masellis[2], Gustavo Saposnik[8], Rick Swartz[2], Carmela Tartaglia[7], Lo

[1]Queen's University, [2]Sunnybrook Research Institute, [3]Western University, [4]University of Ottawa, [5]Baycrest Health Sciences, Rotman Research Institute, [6]Ontario Neurodegenerative Disease Research Initiative, [7]Toronto Western Hospital, [8]St Michael's Hospita

The Ontario Neurodegenerative Disease Research Initiative is investigating six neurodegenerative diseases to characterize neurodegeneration between and within the component patient groups: Alzheimer's disease (AD), mild cognitive impairment (MCI), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and vascular cognitive impairment (VCI). Cross-referencing eye tracking and clinical datasets can further this goal. As a first step, we examined saccade responses in all patient groups and age-matched controls to evaluate their viability as possible biomarkers. We used video-based eye tracking of patients (n=504, age 40-87) and healthy age-matched control subjects (n=133, age 50-93) performing a randomly interleaved pro- and anti-saccade task; the colour of a central fixation point conveyed the instruction for a prosaccade (look at peripheral target) or antisaccade (look away from peripheral target). We assessed parameters including task errors, reaction times, and their association with clinical parameters (e.g. MoCA score). Patients displayed age-controlled abnormalities on subsets of eye tracking parameters (e.g.increased antisaccade direction errors - erroneously looking at peripheral target; increased antisaccade reaction time) relative to controls; patterns of abnormality differed across disease groups (increased saccades away from fixation point in AD/MCI, FTD, and VCI only). These dramatic saccadic changes signify unique behavioural biomarkers for neurodegeneration that can powerfully inform novel diagnostic tools and treatments.

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3-C-68 *Using eye tracking to identify biomarkers of eating disorders in adolescents*

Ryan Kirkpatrick[1], Linda Booij[2], Sarosh Khalid-Khan[1], Douglas Munoz[1]

[1]Queen's University, [2]Concordia University

Of all psychiatric diagnoses, eating disorders (EDs) have the highest mortality rate and while 2.7% of adolescents meet ED criteria, up to 30% of adolescents fully or partially relapse following treatment. Therefore, there is a need to identify biomarkers of EDs to allow for early detection. Saccadic eye movements have been identified as biomarkers in various psychiatric diagnoses including schizophrenia, depression and attention deficit hyperactivity disorder. This study aims to determine whether saccadic eye movements present a biomarker of EDs in adolescents. Patients (12-18 years of age) were recruited from a local outpatient eating disorder treatment clinic and control participants were recruited from the community. All patients met DSM 5 criteria for an ED. All participants completed a well-validated interleaved pro-/anti-saccade task, a free viewing task and clinical questionnaires. The free viewing task consisted of approximately 20 minutes of uninstructed viewing of short video clips with length varying between 2 and 8 seconds, and video clips of food related stimuli were randomly included. Preliminary results indicated a faster reaction time and more anticipatory (<90 ms after stimulus onset) saccades in patients compared to controls on the interleaved pro-/anti-saccade task. Patients had different scan-path behaviours when food stimuli were presented during the free viewing task. Overall, cognitive control of saccadic eye movements appears to differ between adolescents with an ED and controls suggesting their efficacy as a behavioural biomarker for an ED.

3-C-69 *Gene therapy for rescuing epilepsy in Dravet Syndrome*

Yosuke Niibori[1], Shiron Lee[1], David Hampson[1]

[1]University of Toronto

Dravet Syndrome (DS) is a genetic disorder characterized by sudden unexpected death in epilepsy (SUDEP), febrile seizures, and autism-like behaviors. Approximately one in 15,700 individuals is diagnosed with DS between the ages of one and three. DS is anti-convulsive drug resistant and therefore there is no long-lasting, effective treatment available for these patients. Eighty percent of DS patients have loss-of-function mutations in the SCN1A gene, impairing the function of the voltage-gated sodium channel alpha subunit 1 (Nav1.1) that mediates action potentials in neurons. We hypothesize that selectively expressing an adeno-associated virus (AAV) vector encoding a sodium channel subunit in inhibitory interneurons of the CNS will rescue the DS phenotype in Scn1a heterozygous (Scn1a+/-) mice, a model of DS. Scn1a+/- mice have reduced expression of Nav1.1 that impairs the action potential initiation and propagation in

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neurons. Scn1a+/- mice also display characteristics similar to those of DS patients including SUDEP, spontaneous generalized tonic-myoclonic seizures, heat-induced seizures, and autistic features. Treatment of Scn1a+/- mouse pups with the therapeutic vector via injection into the cerebral spinal fluid at postnatal day two resulted in a wide distribution of the transgene in the brain and expression of the sodium channel subunits in GABAergic neurons. The treatment also increased the average lifespan and ameliorated several abnormal behaviors. Our findings indicate that AAV-based gene therapy has therapeutic benefits in a mouse model of Dravet Syndrome.

3-C-70 *The effects of tp5, a cdk5/p25 inhibitor, in human neuroblastoma cell line and c. elegans models of parkinson's disease*

Judith Tran[1], Anika Gupta[1], Harish Pant[2], Bhagwati Gupta[1], Ram Mishra[1]

[1]McMaster University, [2]NIH

Parkinson's Disease(PD) is characterized by impaired motor functions due to the premature death of dopaminergic neurons in the nigrostriatal pathway. Current non-invasive treatments are symptomatic as they only marginally increase striatal dopamine levels but fail to halt/reverse the course of neuronal death. Proactive approaches that could slow the progression of PD and maintain a healthy population of dopaminergic neurons are necessary. CDK5 binds to p25 to induce cell death and this complex is hyperactivated in PD which results in dopaminergic neuronal loss. Research has shown that TP5, derived from p35, has prevented PD like symptoms in an MPTP mouse model. The purpose of this study is to use TP5 to block CDK5/p25 in an in vitro and in vivo model to confirm therapeutic effects, both neuroprotective and neurorestorative, in PD. The human neuroblastoma cell line and the nematode Caenorhabditis elegans were exposed to paraquat(PQ), an oxidative stressor, to exhibit PD's phenotypes. TP5 was administered prior to PQ exposure to determine its neuroprotective effects and after PQ exposure to examine its neurorestorative effects. In the cell line, TP5 was observed to protect neurons using an MTT assay. In the C. elegans system, TP5 demonstrated both neuroprotective and neurorestorative effects when dopaminergic neurons were examined using the Nomarski fluorescence microscopy. Together, these results indicate that TP5 can act as a potential treatment towards PD based on the models that display PD's phenotype by targeting the CDK5/p25 complex.(Supported by CIHR and NSERC, Canada)

3-C-71 *Increased neocortical epileptogenicity in a mouse model of neurofibromatosis type 1*

Azadeh Sabetghadam[1], Chiping Wu[2], Jackie Liu[2], Hongmei Song[2], Liang Zhang[2], Aylin Reid[2]

[1]UHN, [2]University Health Network

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Objectives: Neurofibromatosis type 1 (NF1) is a genetic disorder characterized by cutaneous, skeletal, and neurological findings. Reports of seizures in NF1 are as high as 20%. While seizures are secondary to intracranial lesions in many patients, it is unclear what role the genetic mutation itself plays in seizure predisposition. We hypothesize the Nf1+/- mouse, which does not have intracranial lesions, will demonstrate increased epileptogenicity in response to electrical kindling. Methods: Young adult male and female Nf1+/- mice and wild-type (WT) littermates were used in all studies. Mice were implanted with electrodes for hippocampal or neocortical kindling (n=10/sex/group). Baseline EEG was recorded for up to 48 hours before determination of after-discharge thresholds (ADTs). Mice then underwent two electrical kindling sessions per day. Differences in EEG and kindling parameters between Nf1+/- and WT mice were compared for both hippocampal and neocortical kindling. Results: 50% of Nf1+/- mice had interictal spikes and 15% had spontaneous seizures at baseline versus 0% of WTs. There were no differences in hippocampal kindling parameters, but Nf1+/- mice had lower neocortical ADTs and faster kindling rates. No sex differences were found. Conclusions: These results suggest the genetic mutation in NF1 leads to regional variability in seizure predisposition and contributes to seizures in non-lesional NF1 patients with epilepsy. Future studies will investigate molecular mechanisms involved in increased seizure susceptibility in NF1.

3-C-72 *Targeting the early and late step of cholesterol biosynthesis pathway to promote neuronal regeneration following optic nerve injury*

Alireza Shabanzadeh Pirsaraei[1], Paulo D. Koeberle[1], Philippe P. Monnier[2]

[1]University of Toronto, [2]Krembil Research Institute/University of Toronto

Introduction: CNS injury can result in serious and permanent disability. Therefore, neural regeneration following a CNS injury would have a major impact on the life of affected people. A promising avenue to reduce functional deficits resulting from traumatic damage is to substitute cells lost to injury. Hence, finding effective ways to increase the survival of the cells in the CNS may provide a major treatment method to alleviate impairments. Methods : The present study used adult female rats. The animals were divided into four groups: 1- control 2- Lovastatin (as early stage of cholesterol biosynthesis inhibitor) 3- the combination of Lovastatin and GGPP(Granylgranyl pyrophospahate and 4- AY9944 (late stage cholesterol biosynthesis inhibitor). Optic nerve crush injury was used to investigate axonal regeneration, intraretinal axon integrity and Retinal ganglion cell survival. Axon regeneration of the optic nerve was evaluated based on distance regenerated past the retina: <250 µm, between 250-500 µm and >500 µm. Cell survival was measured and RGC densities (cells/mm2) were g rouped by retinal eccentricity (inner, middle, outer) and expressed asmean ± SEM. Results: Inhibition of the late stage of the cholesterol biosynthesis pathway with AY9944 positively affected optic nerve regeneration , cell survival, and intraretinal axon integrity ($p<0.001$, each) at 21 days following optic nerve crush.

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However, Lovastain failed to improve axon regeneration, cell survival, and intraretinal axon integrity in the same model of axonal traumatic injury. Western blot analysis

3-C-73 *Investigating the neural basis of conditioned analgesia in chronic neuropathic pain*

Chulmin Cho[1], Vassilia Michailidis[1], Batul Presswala[1], Natalia Dziekonski[1], Hyun Been Park[1], Loren Martin[2]

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

Objective: Chronic pain can be interpreted as a maladaptive pain memory that is susceptible to alterations through learning such as conditioning. In support, conditioned analgesia represents a phenomenon where an inert treatment induces pain relief. The objective of the study was to identify the neural pathways of the central nervous system responsible for conditioned analgesia using a mouse model of chronic neuropathic pain. Methods: Mechanical pain thresholds were measured in 6-8wk old male CD-1 mice before and following spared nerve injury (SNI). The SNI mice then underwent a four-day conditioning phase where contextual and tactile stimuli were coupled with an unconditioned drug stimulus (morphine, 10mg/kg). Following the conditioning period, the SNI mice were administered either saline or an opioid receptor antagonist. Following behavioural testing, neuronal activity was mapped in the spinal cord and brain by probing for c-fos expression using immunoblotting and immunohistochemistry. Results: Saline administration following pharmacological conditioning induced analgesia comparable to that of morphine, which was reversed by inhibition of μ-opioid receptors. Immunoblotting and immunohistochemical analyses revealed significant changes in c-fos expression in the spinal cord and the pain processing regions of the brain. Conclusions: We demonstrate a novel animal model of conditioned analgesia within the context of chronic neuropathic pain. This is accompanied by corresponding changes in neuronal activities of the central nervous system similar to those observed in humans.

3-C-74 *Glutamate and GABAergic receptor function in post-concussion syndrome as measured by transcranial magnetic stimulation*

Mitchell Locke[1], Claudia Turco[1], Michel Rathbone[1], Michael Noseworthy[1], Aimee Nelson[1]

[1]McMaster University

Background: Post-concussion syndrome (PCS) affects ~15% of those who incur a concussion, whereby symptoms persist for 3 months or more following injury. Currently there are no conclusive physiological determinants of PCS, although human studies using transcranial

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magnetic stimulation (TMS) have shown that specific gamma-aminobutyric acid receptor (GABAB-R) activity is upregulated long-term in those who have recovered from a concussion. However, research investigating neurotransmitter receptor function in PCS is lacking. Objective: To illuminate whether differences exist in GABAergic and N-methyl-D aspartate receptor (NMDA-R) function in the motor cortex (M1) of those with PCS compared to a non-injured group. Methods: Right-handed individuals with PCS and age- and sex-matched non-injured controls participated. TMS measures of intracortical and transcallosal neurotransmission were performed targeting M1 of the dominant hemisphere, and motor responses were acquired using electromyography in the first dorsal interosseous muscle of each hand. Results: Ten individuals with PCS and 6 non-injured controls participated. NMDA-R activity appears to be greater in the control group. GABAA-R activity may be upregulated in the PCS group, while GABAB-R function seems to be similar between groups. Transcallosal neurotransmission also appears comparable between groups. Conclusion: This study will provide insight into neurotransmitter receptor function in PCS, add to our understanding of PCS pathophysiology, and may reveal future treatment approaches.

3-C-75 *ATF4 mediates amyloid beta-induced neuronal death*

Gillian Petroff[1], Sean Cregan[2]

[1]Western University/Robarts Research Institute, [2]University of Western Ontario

Alzheimer's Disease (AD) is pathologically characterized by amyloid plaques and neurofibrillary tangles. In addition to plaques, amyloid β can aggregate into extremely toxic oligomers that induce neuronal death. High levels of neuronal stress induced by these oligomers might lead to activation of the Integrated Stress Response (ISR). Activation of the ISR leads to translational upregulation of activating transcription factor 4 (ATF4), which can then modulate its downstream pro-apoptotic target genes. Chronic activation of the ISR and prolonged upregulation of ATF4 can potentially result in the neurodegeneration seen in diseases such as Alzheimer's. Previously, it has been found that the phosphorylated form of eIF2α, which is upstream of ATF4 in the ISR, is elevated in AD patients' brains. Therefore, we aimed to determine if amyloid β-induced neuronal death occurs through ATF4-dependent upregulation of pro-apoptotic genes. Primary cortical neurons from ATF4 wildtype and ATF4-null mice were exposed to amyloid β oligomers. Amyloid β treatment induced sustained upregulation in ATF4 protein. In ATF4-null neurons treated with amyloid β, pro-apoptotic transcript levels and apoptotic cell death were both attenuated compared to wildtype neurons ($p > 0.05$). These results suggest that ATF4 plays a necessary role in amyloid β-induced neuronal death, and that targeting the ISR or ATF4 may be a potential therapeutic target for AD treatment.

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3-C-76 *Analyzing the electrophysiological effects of Rett Syndrome on neuronal network development using machine learning*

Milad Khaki[1], Kartik Pradeepan[2], Julio Martinez-Trujillo[3]

[1]Robarts Research Institute, [2]Robarts Research Institute, University of Western Ontario, [3]University of Western Ontario

Rett Syndrome is a genetic neurodevelopmental disorder caused by an MECP2 mutation that results in deficits characteristic of classical autism spectrum disorder. Multielectrode array technology is capable of measuring different aspects of electrophysiological features of the developing neuronal network. However, the amount of data produced is too large to manually explore and extract meaningful patterns. Using a machine learning technique allows us to reduce the amount of redundant information captured during the experiment. Using a supervised statistical classification approach, it is possible to reveal the characteristic differences between normal and Rett syndrome affected cells. Although the higher volume of information encapsulates the different aspects of the problem it also leads to significantly increased observations (big data) and exacerbates the computational complexity. The preliminary results generated by the proposed approach demonstrates that it is possible to rescale the solution to include sufficient number of observations. The results of the pilot experiment show that the differences can be categorized into three distinct developmental periods (early, intermediate, late). These inconsistencies indicate that the rate of growth for Rett syndrome is significantly stunted compared to wildtype, consistent with previous literature. This confirms that the relevant features extracted and selected in the classification process are biological meaningful in distinguishing Rett syndrome.

3-C-77 *Altered connectivity in Rett syndrome human stem cell-derived neural networks*

Rebecca Mok[1], Lyndon Duong[2], Wei Wei[1], Alina Piekna[1], Peter Pasceri[1], Julio Martinez-Trujillo[3], James Ellis[1]

[1]The Hospital for Sick Children, [2]Robarts Research Institute, [3]University of Western Ontario

Induced pluripotent stem cells (iPSCs) provide easily accessible and renewable sources of human cells for in vitro disease modeling applications. We use iPSCs to generate neurons for morphological and electrophysiological study from individuals with the neurodevelopmental disorder Rett syndrome (RTT). RTT is caused by heterozygous mutations in the X-linked gene MECP2, a transcriptional regulator in neurons. We previously reported that RTT neurons have reduced soma area, dendrite length and action potential firing, and we next aim to explore the their ability to form connections within networks. To examine neural circuitry and network synchronicity, we used micro-electrode arrays (MEAs) to record extracellular voltage changes in monolayer cultures twice per week. We compared isogenic pairs of control and MECP2-null

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excitatory cortical neurons differentiated by inducible Neurogenin-2 expression. We showed that RTT neurons have reduced network burst frequency compared to controls at 6 weeks, that could be diminished by AMPAR antagonist treatment. We developed spatial-temporal analysis to evaluate network formation kinetics and map connectivity nodes. We computed spike count correlations at given electrode positions, and preliminary results reveal that correlations decay faster as a function of distance in RTT relative to control networks. Our results show alterations in RTT neural network development using computational MEA approaches, which can form the basis of a drug testing platform aimed at rescuing the observed functional phenotypes.

3-C-78 *Neuro-immune control of post-operative pain via CCR4*

Jaqueline Silva[1], Courtney Bannerman[1], Julia Segal[1], Francisco Gomes[2], Thiago Cunha[2], Ian Gilron[1], Nader Ghasemlou[1]

[1]Queen's University, [2]University of Sao Paulo

Inflammatory pain is a result of complex and dynamic interactions between the immune and the nervous systems. Peripheral inflammation includes the orchestrated recruitment and activation of tissue-resident and circulating immune cells to the site of injury. Our previous studies have identified a central role for Ly6Clo myeloid cells in the pathogenesis of inflammatory pain. We now show that CCL17 and CCL22, chemokines expressed preferentially by these cells, and their cognate receptor CCR4 are key mediators of this response. CCL17 and CCL22 are both upregulated significantly early after tissue injury and elicit a robust acute pain response when administered subcutaneously. Pharmacological blockade of CCR4 using a specific antagonist abrogates this effect. Acute post-surgical pain is also significantly reduced in both transgenic mice lacking CCR4 and wildtype animals treated with a CCR4 receptor antagonist. Together, these results suggest an essential role for the CCL17/CCL22:CCR4 axis in the genesis of inflammatory pain and opens new therapeutic avenues for its control.

3-C-79 *Neuroprotective effect of H2 and H3 relaxins in cultured brain slices deprived of oxygen and glucose*

Brian Wilson[1], Angela Kaiser[1], Nicholas DeAdder[1]

[1]Acadia University

Humans possess two biologically active relaxin peptides (H2 and H3 relaxin). These ligands activate relaxin-family peptide receptors (RXFP) 1 and 3 respectively though cell culture data suggest that both can bind and activate either receptor. Intravenous and intracerebral treatment with human recombinant H2 or H3 relaxin reduces infarct size in two rat stroke models. In the

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current study, organotypic brain slice cultures were prepared using Day 10 neonatal rat tissue. Slices were cultured for two weeks with media changes every 48 hours. Brain slices were placed in one of the following treatments for 60 min: deoxygenated, glucose-free balanced salt solution (OGD) alone (n = 8), or OGD media containing 10-7M H2 relaxin (n = 8), 10-7M H2 relaxin with 10-5M R3 B1-22R (RXFP3 antagonist; n = 8), 10-7M H3 relaxin (n = 8), or 10-7M H3 relaxin with 10-5M R3 B1-22R (n = 8). Control brain slices were placed in an oxygenated balanced salt solution with glucose (n = 8). Slices were returned to normal culture conditions with fresh media for one hour and cell damage/death assess using propidium iodide fluorescence. The main finding from this study is that R3 B1-22R blocked the protective effect of H3 but not H2 relaxin suggesting that activation of both RXFP3 and RXFP1 may be important for protection of neural tissue under ischemic conditions. In a separate experiment, the addition of L-NIL, an inducible NOS inhibitor, to both H2 and H3 relaxin treatments attenuated the effect of both relaxins suggesting that nitric oxide mediates relaxin-induced neuroprotection.

3-C-80 *Fxr1 and mitochondrial function: potential relevance for bipolar disorder*

Aleksandra Marakhovskaia[1], Gianluca Ursini[2], Abbie Wu[1], Jivan Khlghatyan[3], Ana Andreazza[1], Jean Martin Beaulieu[1]

[1]University of Toronto, [2]Lieber Institute for Brain Development, [3]Université Laval

FXR1 is an RNA-binding protein expressed in neurons and is associated with polyribosomes. Recent studies showed an association of genetic variation in the FXR1 locus with bipolar disorder (BD) and comorbid eating disorder. We previously reported (Del'Guidice, 2015) that LiCl chronic treatment increases the level of Fxr1 in the medial prefrontal cortex (mPFC), while Fxr1 overexpression in mPFC mimics LiCl anxiolytic effect in mice.To identify putative Fxr1 targets related to BD we used RIP-seq (RNA-immunoprecipitation) analysis of mRNAs from N2a cells. We obtained immunoprecipitated (IP) RNA samples to identify enriched transcripts in IP samples versus inputs with a cutoff of logFC>0.7 (pFDR-corrected < 0.05). We identified 3366 putative targets of Fxr1 in N2a cell line. Gene ontology overrepresentation analyses highlighted an enrichment of Fxr1 targets in Biological Processes associated with negative regulation of transcription, protein deubiquitination and mitochondrial translation. Further supporting a role of Fxr1 in mitochondrial function, the most overrepresented Cellular Component was mitochondrial inner membrane. We generated CRISPR-Cas9 Fxr1 knock out (KO) cell line to measure mitochondrial change in absence of Fxr1 gene. Relative mtDNA level will be measured in KO cells compared to WT to assess possible functional phenotype alteration of mitochondria. These results converge with studies showing a role of mitochondrial dysfunction in bipolar disorder, suggesting that Fxr1 could be a potential target for the modulation of mitochondrial function in the context of BD.

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3-C-81 *Specifically targeting ERK signaling ameliorates core deficits in mouse models of autism*

Elizabeth Hughes[1], Maryam Khanbabaei[1], Kartikeya Murari[1], Ray Turner[1], Jong Rho[1], Ning Cheng[1]

[1]University of Calgary

The extracellular signal-regulated kinase (ERK) pathway in the brain has been suggested to be critically involved in the pathophysiology of autism spectrum disorder (ASD) and fragile X syndrome (FXS), the leading mono-genetic cause of ASD. Studies have shown that drugs inhibiting ERK signaling, among other potential mechanisms, could rescue disease-modelling phenotypes in rodent models of ASD and FXS. However, the specific role of ERK signaling and the potential therapeutic usage of specifically modulating this pathway have not been determined. It has been demonstrated that ERK signaling is upregulated in the BTBR mouse model of ASD and FMRP-knockout mouse model of FXS. Here, we utilized a specific and potent inhibitor of ERK signaling that passes through the blood-brain barrier well. Our results revealed that ERK activation was robustly reduced in different brain regions, and behavioural deficits modeling core symptoms of ASD were rescued in both mouse models after being treated with the inhibitor, without apparent side effects. Thus, our data suggest that specifically targeting ERK signaling could have therapeutic potential for both ASD and FXS.

3-C-82 *Immune modulating peptide for the suppression of autoimmune cells in Multiple Sclerosis*

Karin Rustad[1], Alexandria Ripplinger[1], Michael Levin[2], Josef Buttigieg[1]

[1]University of Regina, [2]University of Saskatchewan

Multiple Sclerosis (MS) is a debilitating autoimmune disorder of the central nervous system (CNS) affecting over 77,000 Canadians, with a prevalence rate of almost one out of 300 Canadians, with the highest rates in Saskatchewan. Myelination of neuronal axons is essential for the normal and rapid electrical conduction along an axon. Currently there are few feasible options to treat MS. Here, we propose a novel therapy that specifically targets aberrant immune cells. We created a trimolecular peptide (TPC) that combines an antigen sequence (myelin oligodendrocyte glycoprotein; MOG), a modified type IV secretatory system (TIVSS) peptide, and an apoptotic protein. As the TPC displays MOG, the TPC is hypothesized to only bind to immune cells that are actively seeking MOG (e.g. in MS). Since the TPC contains TIVSS, the cell that bound the antigen (e.g. MOG) is forced to take up the TPC. Lastly, the apoptotic protein, which is now inside the cell, causes the cell to undergo apoptosis. Thus eliminating the aberrant cell. In order to test this TPC compound, we induced experimental autoimmune encephalopathy (EAE), in mice, using MOG. Acute administration of the TPC resulted in the suppression of autoimmune cells, as determined

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via flocytometry. We also found significant improvements in motor function as well as a reduction in MS plaque formation in the cerebellum. By targeting the pathogenic immune response whilst leaving the patient's normal immune response intact, we believe this strategy will lead to improved clinical outcomes without the side effects seen in current MS therapies.

3-C-83 *Does voluntary running reduce aberrant seizure-induced hippocampal neurogenesis and improve cognitive behaviours in PTZ kindled rats?*

Kaylea Post[1], Madeline Gilchrist[1], Chantel Cole[1], Lianne Brandt[1], Hugo Lehmann[1], Neil Fournier[1]

[1]Trent University

Chronic epileptic seizures are known to increase levels of hippocampal neurogenesis. However, these new neurons develop and integrate abnormally within the existing networks forming synaptic connections that enhance hippocampal excitability and contribute to cognitive dysfunction. Studies in rodents and humans suggest that voluntary exercise stimulates neurogenesis and can be neuroprotective against the effects of seizures. This study investigates whether voluntary running protects against deleterious effects of repeated seizures induced by the pentylenetetrazole (PTZ) kindling model of epilepsy. PTZ kindled male Long Evans rats were housed in either conventional housing or had access to a running wheel, and were injected every 2 days for 3 weeks with PTZ to induce seizures. Non-kindled controls did not have access to a running wheel during the study. Following kindling, all rats underwent a series of behavioural tests (e.g., open field, elevated plus maze, object recognition, trace fear conditioning). Our preliminary findings show that PTZ kindled runners exhibited superior object recognition compared to PTZ kindled rats and were equivalent to non-kindled controls. Following trace fear conditioning, controls and PTZ runners showed significantly higher levels of freezing during a retention test compared to PTZ kindled rats. We are currently analyzing performance of these groups on emotional measures of depressive-like behaviour (e.g., splash test and forced swim test), and effects of voluntary running during kindling on aberrant seizure-induced hippocampal neurogenesis.

3-C-84 *The role of inflammation in the development of behavioral changes after traumatic brain injury*

Yuqi Lin[1], Chiping Wu[2], Jackie Liu[2], Aylin Reid[2]

[1]University of Toronto, [2]University Health Network

Objectives: Cognitive impairments and motor abnormalities are some of the consequences of traumatic brain injury (TBI). A robust inflammatory response occurs after TBI, with both benefits

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and disadvantages. In experimental TBI models, beneficial effects on behavior have been observed using either pro-or anti-inflammatory strategies. While this may seem contradictory, there has been no direct comparison between the effects of increased and decreased inflammation following TBI. Methods: Adult male Sprague-Dawley rats underwent fluid percussion injury to induce moderate-severe TBI with the following groups: 1) sham injury; 2) TBI; 3) TBI with lipopolysaccharide (LPS); and 4) TBI with minocycline (MINO). Following injury, we administered the composite neuroscores, rotarod, novel object recognition (NOR), and Barnes maze at various timepoints within the first 30 days to detect the role of inflammatory modulation on various behaviors. Results: All TBI groups demonstrated similar levels of neuromotor deficits early after injury as compared to shams. TBI+LPS rats did not recover to the same degree as the TBI group by four weeks post-injury ($p = 0.048$). TBI+MINO rats had better spatial memory than TBI ($p = 0.0339$) and TBI+LPS ($p = 0.0429$). No difference between TBI groups was found in the NOR test. Conclusion: Decreasing inflammation after TBI ameliorated certain TBI-related functional disabilities, while increasing inflammation slowed recovery. This demonstration could serve to develop a potential therapeutic target helping TBI outcomes.

3-C-85 *Viral knockdown of alpha-synuclein expression prevents spreading synucleinopathy*

Sindhu Menon[1], Fadl Nabbouh[1], Kristiana Xhima[1], Pablo Sardi[2], Lamya Shihabuddin[2], Howard Mount[1], Isabelle Aubert[3], Joel Watts[1], Anurag Tandon[1]

[1]University of Toronto, [2]Sanofi-Genzyme, [3]Sunnybrook Research Institute

Objectives: The progressive accumulation of aggregated alpha-synuclein (asyn) in Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) is thought to involve a common prion-like mechanism, whereby misfolded asyn molecules serve as conformational templates for normal asyn that spreads along neuronal pathways. Here, we tested whether therapeutic suppression of asyn expression could reduce the availability of unfolded substrate and thereby disrupt the propagation of pathological asyn. Methods: Brains of hemizygous TgM83 mice, which overexpress human A53T asyn, were stereotaxically injected with adeno-associated virus serotype 1 (AAV1) bearing either eGFP or asyn-shRNA. 30 days later, the animals were inoculated with human MSA-derived brain lysate. Results: Within 3-5 months, the eGFP animals developed widespread and progressive synucleinopathy with increasing motor impairments. In contrast, those animals that received asyn-shRNA had significantly reduced asyn pathology and developed fewer motor deficits. Conclusions: Our data suggests that asyn knockdown confers significant protection against spreading synucleinopathy, even in brain regions distal to the site of asyn knockdown.

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3-C-86 *The pre-symptomatic changes of spinal interneurons in a mouse model of amyotrophic lateral sclerosis.*

Laura Bennett[1], Joanna Borowska[1], Dylan Deska-Gauthier[1], Dallas Bennett[1], Ying Zhang[1]

[1]Dalhousie University

One of the most basic aspects of human life often taken for granted is the ability to move independently. Amyotrophic lateral sclerosis (ALS) is a fatal disease that causes muscle paralysis which eventually halts all bodily movement. Most people with ALS are diagnosed around age 55 and have an average survival rate of only two to five years after diagnosis. Previous efforts in research have found that the characteristic muscle paralysis is caused by the progressive death of motor neurons, most commonly starting in the spinal cord and subsequently, the cerebrum. Currently, key cellular indicators of ALS in mouse models are neuromuscular junction withdrawal and motor neuron cell death which are reported at adult ages postnatal day (P)47 and P90, respectively. Recently published studies in vertebrates have suggested some types of spinal interneurons (INs) may be affected in ALS earlier than motor neuron degeneration. Using a transgenic mouse line, SOD1G93A, as the animal model for ALS, we have compared the distribution and membrane properties of a population of spinal INs that are imperative for rhythmic locomotion termed V3 INs. As early as P21, we observed differences in molecular expression of metabolic transcription factor Nr3B3 and calcium-binding protein Calretinin using immunohistochemistry. Additionally, our data indicated changes of the membrane properties of V3 INs at P14. The early changes we observed in V3 INs may lead to crucial insights for the pre-symptomatic development of the ALS disease and novel diagnostic biomarkers.

3-C-87 *Molecular mechanisms regulating Ca2+ increase in pericytes leading to capillary constriction*

Deborah Villafranca-Baughman[1], Luis Alarcon-Martinez[1], Florence Dotigny[1], Adriana Di Polo[2]

[1]CRCHUM - Université de Montréal, [2]University of Montreal Hospital Research Center

Pericytes are contractile cells that wrap along the walls of capillaries, playing a crucial role in the regulation of capillary diameter and vascular blood flow. Studies suggest that calcium signaling in pericytes and surrounding glia contribute to microvascular dysregulation. In this regard, S100ß is an important regulator of calcium dynamics in astrocytes and might also modulate calcium levels in pericytes. Here, we induce retinal ischemia by ligation of the central retinal artery in transgenic mice carrying the pericyte-specific NG2 promoter driving red fluorescent protein or the genetically encoded calcium indicator GCaMP6. Changes in retinal capillary diameter and intracellular calcium in pericytes were examined using two complementary quantitative approaches: an ex

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vivo stereological setup and a minimally invasive 2-photon microscopy strategy for in vivo imaging. Furthermore, S100ß was quantified by immunohistochemistry, western blots, qPCR and validated by functional analysis. Our data show a reduction in capillary diameter after ischemia and an increase of the intracellular calcium in pericytes. S100ß blockage during ischemia significantly decreased the number of capillary constrictions and capillary diameter was fully reestablished. S100ß was increased 1 fold during ischemia relative to control and changes in electrical activity of bipolar cells were observed after blocking S100ß. Collectively, our data supports an important role of pericytes in capillary constriction during retinal ischemia and suggest that glia-derived S100ß may be involved in this response.

3-C-88 *Antibiotic treatment slows recovery of mechanical hypersensitivity for males but not females in a hindpaw incision model of pain*

Katherine Halievski[1], Michael Salter[1]

[1]The Hospital for Sick Children

Treatment options for chronic pain are limited owing in large part to individual allelic, sex, and microbiota differences. Indeed it is likely that multiple factors together determine individual differences. To explore whether a sex difference exists in the role of microbiota in different painful conditions, we subjected male and female mice to broad-spectrum oral antibiotics for three weeks prior to either a hindpaw incision or a spared nerve injury (SNI). We then assessed pain using a battery of nociceptive behavioural tests: mechanical hypersensitivity, dynamic weight bearing, and thermal hypersensitivity. While all mice responded to the antibiotics as each developed a grossly enlarged caecum, antibiotic treatment alone did not alter mechanical or thermal sensitivity. However, after hindpaw incision we found that mechanical withdrawal thresholds of male mice showed slower recovery to baseline than those of vehicle-treated males. Antibiotic-treated males also showed an increased rear-load in dynamic weight bearing testing compared to vehicle-treated males. Thermal hypersensitivity did not differ between vehicle- and antibiotic-treated males. After SNI, vehicle- and antibiotic-treated male mice showed no behavioural differences using this battery of tests. Antibiotic-treated female mice were not different than vehicle-treated females in any assay after either hindpaw incision or SNI. Thus, long-term antibiotic treatment affects behavioural responses in an acute pain model in a sex-specific manner.

3-C-89 *Neuroligin 1 is altered by amyloid-beta oligomers and modulates their toxicity*

Julien Dufort-Gervais[1], Chloé Provost[1], Laurence Charbonneau[1], Christopher Norris[2], Frédéric Calon[3], Valerie Mongrain[4], Jonathan Brouillette[1]

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[1]Hôpital du Sacré-Coeur de Montréal, [2]University of Kentucky, [3]Université Laval, [4]Université de Montréal

Synapse loss and ensuing neurodegeneration are the best predictors of cognitive decline in Alzheimer's disease (AD). We know that soluble amyloid-beta oligomers (Abeta) are involved in synapse loss when they begin to accumulate in the brain 10 to 15 years before clinical symptoms. However, we still ignore which synaptic molecule is altered at the onset of AD when Abeta level starts to increase in the brain. In this context, finding changes in the level of a molecule inherently involved in synapse functioning and stabilization could be a useful biomarker and a potential therapeutic target in the pre-symptomatic state of AD. NLG1 is a post-synaptic adhesion protein that interacts with the pre-synaptic proteins neurexin, and is exceedingly important for synapse formation, maturation, maintenance, and plasticity. Moreover, NLG1 has been shown to be involved in many cellular events changed in AD, such as the function of the NMDA receptors, synaptic plasticity, memory performance, and sleep regulation. Here we found that protein levels of NLG1 are decreased in the hippocampus of the 3xTgAD mouse model as well as in individuals with mild cognitive impairment (MCI) and AD patients. Lower NLG1 levels also correlated with poorer cognitive score in the mini-mental state examination (MMSE) and higher levels of soluble Abeta in MCI and AD patients. Cell death and memory deficits induced by chronic hippocampal injections of Abeta were amplified in NLG1 knockout mice. Altogether, these data suggest that NLG1 is altered by Abeta and modulates their toxicity.

3-C-90 *Identifying neurons active in the motor cortex when performing behavioral tasks during stroke recovery*

Damian Chwastek[1], Yingben Xue[1], Greg Silasi[1], Diane Lagace[1]

[1]University of Ottawa

Stroke is a leading cause of disability in Canada, with over 400,000 Canadians living with stroke-induced disabilities. Stroke survivors experience partial recovery for a limited time following their stroke due to a phenomenon known as spontaneous biological recovery (SBR). It is hypothesized SBR is in part due to the remapping of cortical functions controlling motor behaviour. However, it has been a challenge to identify with high temporal and spatial specificity whether the same or different cellular circuits are utilized in the motor network following stroke. This study identifies the active network of motor cortex neurons when performing a motor task through the use of an inducible Arc-CreERT2:Rosa-YFPf/f mouse model. Specifically, neurons that are active during performance of the bimanual string pull task are labeled before versus after stroke, as well as during SBR following photothrombosis-induced stroke. Our results show that the string-pull test is effective in measuring deficits following stroke and the model is able to differentiate between controls and mice that are performing the test. By elucidating the network of cells that are utilized

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during stroke recovery, this work aims to open the door for harnessing these cells to develop new therapies for stroke survivors.

3-C-91 *Robotic assessment of upper limb function in a non-human primate model of chronic stroke*

Yining Chen[1], Bruno Cohen[1], Joseph Nashed[1], Douglas Cook[1]

[1]Queen's University

Stroke is the leading cause of death and disability and has the largest socioeconomic burden of any disease in Canada. Survivors are frequently left with long-term disabilities that diminish their autonomy and quality of life and result in the need for chronic care. As such, there is an urgent need for the development of therapies that improve stroke recovery, as well as accurate and quantitative tools to measure function. Non-human primates closely resemble humans in neuroanatomy and upper limb function, and may be crucial in bridging the translational gap for testing stroke therapies. In this study, cynomolgus macaques were trained on a visually guided reaching task and a postural task on the Kinesiological Instrument for Normal and Altered Reaching Movements (KINARM). We then induced strokes in these animals by transiently occluding the middle cerebral artery for 90 minutes and assessed their motor performance on the same motor tasks throughout recovery. During the weeks following stroke, we noted recovery of function that plateaued by two months post-stroke. In comparing performance in this chronic stroke state to performance pre-stroke, we found that hand movements became slower, less accurate, and less stereotyped, similar to deficits revealed in the same motor task in human stroke patients. Taken together, these studies highlight specific sensorimotor deficits in visually guided reaching movements following stroke and validate the use of robotic assessment tools in a non-human primate model of stroke in identifying and quantifying such deficits.

3-C-92 *Investigating the role of RGM family and their receptor neogenin on multiple sclerosis through experimental autoimmune encephalomyelitis*

Seunggi Lee[1], Philippe Monnier[1]

[1]University of Toronto

Introduction: It has been speculated that Respulsive Guidance Molecule a (RGMa) and its receptor Neogenin plays an important role in many cellular events leading to multiple sclerosis (MS) development. Therefore, using the most commonly used and best characterized animal model of MS, Experimental Autoimmune Encephalomyelitis (EAE), RGMa and Neogenin's interaction and their detrimental effects to MS patients have been investigated. Methods : This study involves a

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transgenic mice line, Neogenin KO. EAE was induced to C57BL/6 female mice aged 6-8 weeks Neogenin KO mice and WT mice by injecting mice with 100ug of Myelin Oligodendrocyte Glycoprotein peptides (MOG) and complete Freud's adjuvant mixture subcutaneously on day 0. Then 400ng of pertussis toxin was injected intraperitoneally on day 0 and day 2 post induction as a booster injection. Mice were scored daily until day 18 post immunization, then spinal cords were collected to be imaged. Results : Neogenin KO mice exhibited significantly reduced severity of EAE symptoms compared to WT group. Spinal cords of both groups were sectioned and stained for fibrinogen to visualize blood toxin extravasation into spinal cords of EAE induced mice. Fibrinogen signal intensity was significantly reduced in Neogenin KO mice. Light-sheet fluorescence microscope images of the same spinal cords revealed significant difference in leakage profiles as well. Conclusion: These results strongly supports the detrimental role of RGMa-Neogenin interaction to development of MS and illuminates potential therapeutic target for the MS patients.

3-C-93 *Role of interleukin-1β in the development of pain hypersensitivity in a model of non-compressive disc herniation*

Milind Muley[1], Yu Shan Tu[2], Benjamin Steinberg[2], Michael Salter[1]

[1]The Hospital for Sick Children, [2]Research Institute at The Hospital for Sick Children (SickKids)

Low back pain secondary to disc herniation is a major health problem. Proinflammatory cytokines have been implicated in the pathogenesis of disc herniation. Here, we assessed the contribution of interleukin-1β (IL-1β) to the development of pain behaviour in a recently developed model of non-compressive disc herniation. Nucleus pulposus (NP), collected from littermate tail intravertebral discs, was placed on the sciatic nerve of male C57BL/6 mice. In sham animals, only the sciatic nerve was exposed. We found that mechanical allodynia, measured by von Frey filaments, appeared on day 1 and persisted to day 7 following NP exposure to the sciatic nerve. Using immunohistochemistry, we detected an increase in macrophage (F4/80) infiltration in and around the nerve at 1-week post-surgery in NP animals, compared with sham controls. We identified increased IL-1β gene expression by PCR in the sciatic nerves treated with NP compared with sham controls. Treatment of NP animals with a caspase-1 inhibitor, VX-765 (200 mg/kg i.p.; days 0-3), prevented mechanical allodynia as compared to vehicle-treated animals. To gain mechanistic insight, we have developed an in vitro assay to test the effect of VX-765 on IL-1β secretion from cultured human macrophages. It was observed that VX-765 prevented the release of IL-1β from the cultured macrophages. These results indicate an important role for IL-1β secretion from macrophages during the development of pain associated with non-compressive disc herniation. Blocking IL-1β may be a viable strategy in treating pain associated with disc herniation.

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3-C-94 *A longitudinal analysis of depression and anxiety in Parkinson's disease*

Margaret Prenger[1], Nicholas Handfield-Jones[1], Penny MacDonald[1]

[1]University of Western Ontario

Parkinson's disease (PD), a neurodegenerative disorder characterized by loss of dopaminergic neurons in the basal ganglia, is commonly recognized for its motor symptoms (e.g., tremor, rigidity). These motor symptoms are treated well with dopamine replacement medication (e.g., L-DOPA); however, many of the lesser-known non-motor symptoms do not respond with the same success. Unfortunately, this includes depression and anxiety, which are highly prevalent in PD and contribute to reduced quality of life. However, the mechanisms underlying depression and anxiety in PD are currently unknown and are complicated by a variety of disease factors, including L-DOPA. In this study, depression and anxiety symptoms of a large sample of PD patients (n = 114) and healthy controls (n=60) were longitudinally evaluated. All participants completed the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) at several time points. Furthermore, participants were tested both ON and OFF L-DOPA at each time point. Using a mixed-models approach, we evaluated the severity of affective symptoms in PD compared to controls, as well as the influence of other factors such as medication and disease progression. Compared to controls, PD patients experienced higher BDI and BAI scores and a worsening of depression, but not anxiety, over time. Interestingly, controls showed reduced BAI scores while ON L-DOPA, while medication had no effect for PD patients. These results elaborate on the complex and progressive nature of affective symptoms in PD and might help inform future treatment approaches.

3-C-96 *Selective knockout of amyloidogenic regions in SOD1 modulate its aggregation and toxicity in living cells*

Jeremy Nan[1], Luke McAlary[2], Neil Cashman[3]

[1]University of British Columbia, [2]University of Wollongong, [3]University of British Columbia, Djavad Mowafaghian Centre for Brain Health

Background: ALS is a neurodegenerative disease that causes the death of motor neurons, leading to gradual paralysis of the body. Cu/Zn superoxide dismutase (SOD1) mutations account for 20% of all familial cases of ALS. Misfolded mutant SOD1 can induce the misfolding of wild-type SOD1 and this propagation can occur intercellularly, similar to the properties of prion conversion. Mutant SOD1 has also been shown to form aggregates in patient tissue. A recent study has identified that SOD1 contains four fibril-forming segments that could be involved in its aggregation. We therefore hypothesized that by disrupting the tertiary structure of these fragments we may be able to decrease the aggregation propensity of the protein. Methods and Materials: We generated a SOD1 G85R-GFP reporter construct that can be transfected into HEK293 cells to model and track

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its aggregation. The amino acid sequence of mutant SOD1 (G85R) was subjected to multiple predictive algorithms to extrapolate seven aggregation prone segments within the protein. Proline mutations were added to the constructs to disrupt these regions of the protein. Results: Disruption of all seven aggregation prone segments led to the complete ablation of SOD1 G85R-GFP aggregation. Segments closer to the N-terminus had a greater importance in the aggregation of the protein, as their disruption led to lowered aggregation compared to those in the C-terminus. Significance: By identifying these regions we may further understand why SOD1 aggregates in disease as well as provide targets for chemical or immune therapies.

3-C-97 *Motor impairment in mice with a gain-of-function mutation in retinoic acid receptor beta (RARB).*

Nicolas Lemmetti[1], Christina Nassif[1], Jacques Michaud[2]

[1]CHU Sainte-Justine Research Center/Université de Montréal, [2]CHU Sainte-Justine Research Center/Université de Montréa

Retinoic acid (RA) plays a critical role during brain development by binding to receptors that function as ligand-activated transcription factors. We previously described mutations in the retinoic acid receptor beta gene (RARB) in patients with dystonia. We found that these mutations enhance RA-induced transcriptional activity 2- to 3-fold over the WT receptor, suggesting a gain-of-function (GOF) mechanism. Loss of Rarb in mice cause motor impairment and a reduction of striatonigral neurons due to premature differentiation of their progenitors. We hypothesize that the motor impairment of patients with RARB GOF mutations is caused by increased RARB signaling in the striatum, possibly disrupting homeostatic control of the same pathways as those affected by decreased Rarb signaling. In order to investigate this hypothesis, we introduced p.R394C, the equivalent of the recurrent p.R387C GOF mutation found in some patients, at the Rarb genomic locus in mice. Behavioral assessment of RarbR394C/+ mice showed a short stride and dramatically reduced motor coordination in the rotarod paradigm. Moreover, these mice show a decreased number of D2- but not D1-expressing neurons in the striatum. Rarb-R394C/R394C mice are born at the expected mendelian ratio but they show a waddling gait, their growth is compromised and they die perinatally. In order to understand the cellular basis of the motor impairment associated with p.R394C, we are currently characterizing the striatum of Rarb-R394C/+ and Rarb-R394C/R394C mice using additional molecular markers and transcriptomic studies.

3-C-99 *Assessing the effect of one minimal dose of risperidone vs olanzapine on the drive to play extraordinary social roles associated with disorganization*

Ilya Demchenko[1], Gifty Asare[2], Efthymios Hadjis[1], Ola Mohamed Ali[1], J. Bruno Debruille[1]

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[1]McGill University, [2]York University

Consistent with the behavioural conflicts they generate, personal drives to play extraordinary (E) social roles (SRs) were found to be an independent factor predicting disorganization measured by the Schizotypal Personality Questionnaire (SPQ). Here, we compared the effect of risperidone vs olanzapine on those drives. Healthy participants (Pps) received either 1.0 mg of risperidone (risp, n = 45) or 2.5 mg of olanzapine (ola, n = 46). Pps were tested before (session 1, S1) and during (session 2, S2) the effect of those medications. They saw 200 SR names at S1 and 200 other SR names at S2. SRs were extraordinary (E) or ordinary (O), and favourable (F) or not (unF). For each SR, Pps had to decide whether or not they would consider performing it at any moment of their life. Pps were divided into high- and low-ESR acceptors (HAESRs & LAESRs) using a median split of the percentages (%) of ESRs they accepted. HAESRs who took ola became significantly faster at rejecting EF SRs ($p = .003$) and EunF SRs ($p = .02$) and at accepting OF SR ($p = .001$) than risp HAESRs. From S1 to S2, ola HAESRs accepted a significantly smaller % of F ESRs ($p = .0004$). The % of accepted OF SRs significantly decreased in risp HAESRs ($p = .0007$) across sessions while it remained stable in ola HAESRs ($p = .24$). This difference was significant across medication groups ($p = .002$). A single minimal dose of olanzapine thus appears to increase the drive to play ordinary roles and to decrease the drive to play the extraordinary ones. Olanzapine might thus be better at dampening disorganization than risperidone.

3-C-100 *Investigating the therapeutic role of CDNF and MANF upon Lurasidone treatment in a MK-801 model of schizophrenia*

Brendan Fera[1], Todd Hoare[1], Ram Mishra[1]

[1]McMaster University

Increasing evidence supports the notion that schizophrenia (SZ) is a subtle disorder of brain development and plasticity. Neurotrophic factors (NTFs) are naturally occurring endogenous secretory proteins that play an important role in the differentiation, maintenance, and survival of neurons. Mesencephalic astrocyte-derived neurotrophic factor (MANF) and cerebral dopamine neurotrophic factor (CDNF) are two NTFs that support the survival of midbrain dopaminergic neurons. Lurasidone Hydrochloride (LUR) is a novel atypical antipsychotic drug with a strong affinity for dopamine D2 and serotonin 5-HT2A receptors and is hypothesized to improve cognition in patients with SZ. In this study we sought to investigate the effects of LUR treatment on CDNF and MANF expression in a MK-801 model of SZ. Wistar rats were pre-treated with LUR (3.0 mg/kg i.p.) followed by MK-801 (0.35 mg/kg i.p.) for 10 days. On days 8 and 9 rats were subjected to a series of behavioural paradigms to test for a distinct class of symptom. Rats were sacrificed one hour after the last injection on day 10 and the striatum, prefrontal cortex, cortex, substantia nigra, and hippocampus were harvested for analysis. mRNA expression of CDNF and MANF was quantified using RT-qPCR. We show that LUR successfully attenuated MK-801-induced psychotic,

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social, and cognitive deficits. Further, we show that treatment with LUR upregulates MANF mRNA expression in the prefrontal cortex. Our results reinforce the procogntive properties of LUR and will aid in further elucidating the therapeutic role of NTFs in SZ.

3-C-101 *Activation of Choroid Plexus Transient Receptor Potential Vanilloid Channel-4 channels stimulates brain EGF secretion and recovery*

Anil Zechariah[1], Marco Prado[1], Rithwik Ramachandran[1]

[1]University of Western Ontario

Stroke is a leading cause of death and disability. There are few treatment options for stroke patients and new therapeutic strategies are sorely needed. A promising approach for promoting recovery after stroke is through enhancing endogenous repair mechanisms in the brain, such as through stimulating the production of neurogenic and/or angiogenic factors. The choroid plexus (CP), a vascularized epithelial structure floating within the brain ventricles, is a critical player in this regard as it produces the cerebrospinal fluid and other factors that maintain brain homeostasis. Transient Receptor Potential Vanilloid-4 (TRPV4) is a non-selective cation channel, originally described as a sensor of changes in osmolarity. Using a novel transgenic Trpv4-lacZ reporter mouse we observed high levels of TRPV4 expression in the cells of CP and ependymal layer of the sub-ventricular zone. We hypothesized that TRPV4 activity in CP and ependymal cells might promote the secretion of neuroprotective factors that aid recovery. Ex-vivo experiments demonstrated that a small molecule TRPV4 agonist increase CP calcium signalling and significantly increased the secretion of epidermal growth factor (EGF), a key regulator of neural stem cell function. In-vivo genetic deletion of TRPV4 influenced the progression of tissue injury after experimental stroke. Ongoing work is examining whether targeting TRPV4 influences post-stroke functional recovery. We have identified TRPV4 as a potential therapeutic target for influencing CP function and to promote functional recovery of the injured brain.

3-C-102 *Effects of repeated awake closed head injury on cell proliferation and neurogenesis in juvenile rats*

Katie Neale[1], Hannah Reid[1], Barbara Sousa[1], Brian R Christie[1]

[1]University of Victoria

Traumatic brain injury (TBI), is becoming increasingly recognized as a global health issue. Each year over 160,000 Canadians experience some form of TBI and around 1.5 million Canadians are currently affected by a TBI. Children are especially susceptible to repeat head injury and represent an at risk population for sustaining sports-related concussions. Learning and memory dysfunction

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are common sequelae of TBI, which is likely a result of damage to the hippocampus, a structure that is particularly vulnerable to insults to the brain. This study uses a novel awake closed head injury (ACHI) model in juvenile rats to investigate injury-induced changes to the neurogenic niche following repeated mild traumatic brain injury. Following 8 repeated ACHIs, rats were injected with BrdU and then sacrificed 2 hours later on post injury day 1, 3 or 7. BrdU was used to identify mitotically active cells at those specific time points in addition to ki-67, an endogenous marker for proliferation, DCX, a marker of mature neurons and NeuroD, a marker of late stage progenitors. Preliminary results showing increased cellular proliferation indicate that future studies taking advantage of a repeated awake injury model will help further our understanding of potential innate repair mechanisms in the juvenile brain following repeat traumatic brain injury.

3-C-103 *Association between depression severity and hippocampal volumes in Vietnam war veterans with PTSD, TBI, both or neither*

An Li[1], Sonja Stojanovski[1], Arielle Levy[1], Gabriel Devenyi[2], Mallar Chakravarty[2], Anne Wheeler[1]

[1]The Hospital for Sick Children, [2]Douglas Institute, McGill University

Background: High comorbidity is found between post traumatic stress disorder (PTSD), traumatic brain injury (TBI) and depression. Reduced hippocampal volume has been associated with all three conditions suggesting the etiology and neural basis of these disorders may overlap. The objective of this study was to examine whether the association between depression severity and hippocampal volume is moderated by the presence of TBI or PTSD. Methods: The Alzheimer's Disease Neuroimaging Initiative - Department of Defence (ADNI-DOD) dataset of aging veterans was used for the study. Volumes of hippocampi and extrahippocampal white matter projections were computed using the MAGeT brain segmentation pipeline in male veterans with PTSD (n=59), TBI (n=24), PTSD&TBI (n=34), and healthy aging controls (n=55). The relationship between depression severity measured with the geriatric depression scale and hippocampal volumes, as well as moderation by TBI and PTSD were assessed. Results: A negative association between left hippocampal volume and depression severity in veterans was moderated by the presence of PTSD such that in the two PTSD groups there was no association between hippocampal volume and depression severity. Conclusion: Distinct neural bases of depression severity in veterans with TBI and PTSD indicate dissimilar etiology of depression symptoms that may benefit from different types of treatments.

3-C-104 *Transplantation of human spinal oligodendrogenic neural progenitor cells enhances remyelination and functional recovery after traumatic spinal cord injury*

Mohamad Khazaei[1], Christopher Ahuja[1], Hiroaki Nakashima[1], Narihito Nagoshi[1], Michael Fehlings[2]

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[1]University Health Network, [2]University of Toronto

The harsh microenvironment generated after traumatic spinal cord injury (SCI) results in significant early necrotic and apoptotic cell death. Oligodendrocytes are particularly susceptible to the death after injury and are one of the first cell types which die resulting in widespread demyelination of both injured and spared axons. Cell replacement therapy with neural progenitor cells (NPCs) represents a promising therapeutic potential for SCI, however, the proportion of NPCs differentiated to oligodendrocytes after transplantation is very low. This is more dramatic for human cells. We have developed a unique method to bias the differentiation potential of tripotent human NPCs towards more oligodendrogenic fate (oligodendrogenic NPCs; oNPCs) while preserving their potential to generate neurons and astrocytes. In clinically-relevant models of rodent cervical and thoracic clip-contusion SCI, we studied the effects of these novel cells on lesional area, graft-host integration, and functional recovery. Transplanted oNPCs migrated rostrocaudally along spinal cord and differentiated into NeuN+/Tuj1+ neurons and GFAP+ astrocytes as well as Olig2+ immature and GST-pi+ mature oligodendrocytes. Mature human oligodendrocytes also expressed MBP and integrated with rodent NF 200+ neuronal axons, indicating the potential of transplanted oNPCs to remyelinate host axons in both the cervical and thoracic spinal cord. Furthermore, oNPC transplanted rats demonstrated significantly reduced lesion volumes and enhanced tissue preservation, white matter sparing and motor functional recovery. This w

3-C-105 *A self-assembling peptide biomaterial to optimize human neural stem cell-based regeneration of the injured spinal cord*

Christopher Ahuja[1], Mohamad Khazaei[1], Zijian Lou[2], Yao Yao[2], Ali Hasan[2], Vjura Senthilnathan[2], Inaara Walji[2], William Luong[2], Alexander Post[2], Gokce Ozdemir[2], Edward Robinson[2], Priscilla Chan[2], Jian Wang[2], Michael Fehlings[2]

[1]University Health Network, [2]University of Toronto

Introduction Human induced pluripotent stem cell-derived neural stem cells (hNSCs) are a promising approach spinal cord injury (SCI). Unfortunately, the harsh post-injury microenvironment impairs regeneration. QL6 is a novel, biodegradable peptide capable of self-assembling into an extracellular matrix-like lattice in vivo. Early evidence suggests it may support cell-based CNS regeneration. Objective Assess QL6's ability to support translationally-relevant hNSCs to regenerate the chronically injured spinal cord. Methods hNSCs were grown on QL6 versus Geltrex control. qPCR and an EDTA assay were used to determine mechanisms of cell adhesion. hNSC survival, proliferation (Ki67), and neurosphere formation was extensively characterized in vitro. T-cell deficient rats underwent a clinically-relevant C6-7 clip-contusion SCI. In the chronic phase, animals were randomized: (1)vehicle, (2)hNSCs transplant, (3)QL6, (4)QL6+hNSCs. All rats received rehabilitation. Results hNSCs proliferated robustly on QL6

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versus geltrex as shown by Ki67+ labelling (29vs6%;p<0.01). EDTA assay suggested that human NSC-QL6 binding is largely Ca-independent. hNSCs cultured on QL6 downregulated apoptosis markers, upregulated pro-neuronal markers and select Ca-independent cell adhesion molecules. QL6 also promoted adherent neurosphere formation, the native conformation of NSCs. Blinded rat sensorimotor assessments are ongoing. Conclusion This work provides key proof-of-concept data that a self-assembling biomaterial could support translationally-relevant human iPS-NSCs for use in SCI.

3-C-106 *OPTOGENETIC-mediated spatiotemporal control of protein aggregation to study*

Morgan Bérard[1], Abid Oueslati[2]

[1]CHUL, [2]Université Laval & CHU de Québec Research Center, Neuroscience Axis

Protein aggregation into insoluble deposits is the paramount pathological hallmark of several neurodegenerative diseases. One example is α-synuclein-rich inclusions, also called Lewy bodies (LBs), found in α-synucleinopathies. However, how these aggregates affect neuronal homeostasis leading to neurodegeneration remains elusive in part because we lack the proper tools to undertake such investigations. Our team has created an innovative technology that will allow us to obtain a better understanding of the mechanisms leading to the formation of these pathological forms and how these propagate in the brain. This optobiology-based tool controls the aggregation and propagation of α-syn under light control (the LIPA system: light-inducible protein aggregation). We used a gene therapy approach, based on the use of adeno-associated virus (AAV) to overexpress our system directly in the striatum of naive mice. To deliver the light needed to induce the aggregation and propagation of α-syn, we used implantable micro-devices developed in collaboration with Dr. Jeong. Our system allowed to induce stable inclusion formation of α-syn with spatial and temporal control in living cells. Leading for the first time, in vivo formation of inclusions faithfully mimic several authentic features of LBs. This system constitutes a new and exceptional tool by which to generate, visualize and dissect the role of protein aggregates in neurodegeneration. This understanding will help develop new effective curative treatments to cure or even prevent the onset of this disease.

3-C-107 *The adaptor protein p66Shc regulates CNS cell metabolism and redox state via the KEAP1-Nrf2 axis*

Asad Lone[1], Robert Cumming[1]

[1]University of Western Ontario

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The amyloid hypothesis has dominated drug discovery in Alzheimer's disease (AD) for the last 20 years, despite the fact that clinical trials evaluating the efficacy of agents which target amyloid have been unsuccessful. A significant proportion of the elderly population have extensive amyloid beta (Aß) deposition within their brains, yet show no symptoms of dementia, suggesting that some cells are resistant to Aß toxicity. Several studies have shown that CNS cells selected for resistance to Aß toxicity exhibit lower ROS levels and a metabolic shift from mitochondrial dependent oxidative phosphorylation (OXPHOS) to aerobic glycolysis to meet their energy needs. Expression & activation of the adaptor protein p66Shc promotes OXPHOS and increases ROS production. However, the mechanism by which p66Shc mediates this metabolic shift is unknown. We have previously shown that expression & activation of p66Shc in neuronal and glial cells represses glycolytic enzyme expression while increasing OXPHOS and ROS levels. Knockdown of endogenous p66Shc promoted aerobic glycolysis and reduced intracellular ROS levels. Activation of p66Shc increased sensitivity to Aß toxicity, whereas silencing p66Shc protected cells from Aß insult. In preliminary studies, we have discovered that p66Shc expression and activation suppresses upregulation of the transcription factor Nrf2 by increasing protein levels of KEAP1, a negative regulator of Nrf2. Thus, p66Shc expression may control the redox state of CNS cells via the KEAP1-NRF2 pathway, and represent a potential therapeutically relevant target for AD.

3-C-108 *Dynamic networks of EEG sources enhance localization of the epileptogenic zone*

Daniel Jacobs[1], Jose Martin del Campo[2], Peter Carlen[3], Yotin Chinvarun[4], Berj Bardakjian[1]

[1]University of Toronto, [2]Toronto Western Hospital, [3]Krembil Research Institute, [4]Phramongkutklao Hospital

Objective: Dynamic networks of cross-frequency coupled (CFC) signals extracted from intracranial EEG (iEEG) and scalp EEG recordings enhance localization of the epileptogenic zone (EZ) in patients eligible for surgical resection. Methods: EEG and iEEG recordings were obtained from 6 subjects undergoing presurgical monitoring from Toronto Western Hospital, Canada, or Phramongkutklao Hospital, Thailand. CFC signals were generated by applying a continuous wavelet transform to the EEG, and then coupling the phase of low frequency signal components with the amplitude of high frequency signal components. Source imaging using minimum-norm estimates was performed on scalp EEG. Dynamic networks for iEEG channels and scalp EEG source imaging nodes were assessed by connectivity measures including adaptive partial directed coherence (aPDC). Graph theoretic measures including in-betweenness centrality were used as network metrics. Networks properties were compared over various seizure states for both EEG and iEEG, and for raw EEG and their extracted cross-frequency coupled signals. Results: Network properties highlight seizure activity surrounding the EZ in both iEEG and scalp EEG. Connectivity applied to CFC signals extracted from EEG and iEEG improves specificity of

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localizing the EZ. Conclusions: Dynamic networks of CFC signals are a useful tool for aiding in the presurgical localization of epileptogenic zones.

3-C-109 *Expression profile of angiogenic factors and their role in Amyotrophic Lateral Sclerosis (ALS) disease pathology*

Akshay Anand[1], Shweta Modgil[1], Radhika Sharma[1], Abha Tiwari[1], Kaushal Sharma[1]

[1]Postgraduate Institute of Medical Education and Research

Introduction: ALS is a rare disease with progressive degeneration of motor neurons with prevalence of 6 in 100,000 individuals. In severe stages of the disease, patient dies because of respiratory failure. Only 10% of cases are found to be familial while almost 90% of the cases are sporadic. Various molecules have been studied in relation with disease pathology and progression. In the present study we tried to determine the protein expression of angiogenic markers i.e. vascular endothelial growth factor (VEGF), VEGF receptor-2 (VEGFR2) and angiogenin (ANG). The potential of these factors as future biomarkers for disease diagnosis was assessed. Methodology- 89 patients and 98 controls were recruited for the study as per approval of institutional ethical committee (IEC). ELISA was performed on plasma for candidate proteins for analysing the protein levels. Expression profile of patients and controls was compared using independent t-test and value with <0.05 were taken as significant. After analysing protein levels correlation analysis between the proteins was done. Results: Protein levels for all factors were found to be significantly reduced in ALS patients when compared with controls. Correlation analysis of the proteins suggests that one protein influence the expression of other. Conclusion: Expression of angiogenic factors is altered in ALS and can be further studied for potential markers in larger cohort.

3-C-110 *Plasma and cerebrospinal fluid (CSF) levels of marker proteins in Amyotrophic Lateral Sclerosis (ALS) patients.*

Shweta Modgil[1], Radhika Khosla[1], Abha Tiwari[1], Akshay Anand[1]

[1]Postgraduate Institute of Medical Education and Research

Introduction: ALS is a fatal disease characterised by progressive degeneration of motor neurons. Genetic link for the disease has been established, however, it accounts for only 10% of cases. Sudden onset of disease in sporadic cases has led to study of expression profile of proteins associated with the disease. Marked variation has been reported in expression of these molecules by different researchers. Therefore, in the present study we determined the plasma and CSF

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levels of three protein markers i.e. Optineurin, TDP-43 (Tar DNA binding protein) and MCP1 (Monocyte Chemoattractant Protein-1) in ALS patients. Methodology- ALS and controls from North Indian population were recruited with proper ethical approval and patient consent. Blood (for plasma) and CSF were collected for protein analysis and ELISA was performed in both (plasma and CSF) for candidate proteins. Protein levels in ALS and controls were compared using independent t-test. Results: Levels of TDP43, MCP1 and optineurin were found to be significantly altered in plasma and CSF of ALS patients. Conclusion: Plasma and CSF levels of marker proteins in ALS patients can be associated with disease onset in sporadic cases. Longitudinal follow up study can be helpful in determining the role of these proteins in disease progression.

3-C-111 *Study of handwriting on a graphic tablet for the aid of early diagnosis of Alzheimer's disease in a Moroccan population*

Aboulem Ghita[1]

[1]Service de Neurologie, Centre Hospitalier Universitaire Hassan II-Fès

Introduction: Handwriting is a complex component of human language that occurs later in language acquisition. Previous literature discussed the changes in both graphic and cinematic characteristics of handwriting. Besides Alzheimer's disease, many neurodegenerative pathologies are characterized by progressivedisorganization of handwriting. Depending on the cognitive stage of dementia, the graphic gestures deteriorate just like the spatial construction. Objectives: We study the characteristics of Arabic handwriting in a healthy Moroccan population and compare it to individuals with Alzheimer's disease (IWA). Our goal is to develop an innovative technique to help healthcare professionals detect cognitive deterioration using handwriting analysis. Methods: The handwriting is captured on a WACOM graphic tablet and thenanalyzed online as a sequence of acquired signals (pressure, speed and inclination of the pen). Result: we conducted a primary analysis with 19 individuals with Alzheimer and 19 control subjects for age. Level of education and handedness. The results reveal significant slow down in speed and acceleration for IWA compared to control subjects, and a higher rate of hesitations. Conclusion: These preliminary results allow us to identify discriminant characteristics through the analysis of various writing parameters with the goal of identifying clusters of handwriting characteristics.

3-C-112 *Increased expression of schizophrenia-associated gene C4 leads to miswiring of prefrontal cortex and reduced social interaction*

Tushare Jinadasa[1], Ashley Comer[1], Lisa Kretsge[1], Thanh Nguyen[1], Jung Joon Lee[1], Elena Newmark[1], Frances Hausmann[1], SaraAnn Rosenthal[1], Kevin Lui Kot[1], William W. Yen[1], Alberto Cruz-Martin[1]

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[1]Boston University

Schizophrenia is a serious devastating mental illness affecting close to 1% of the general population. Individuals affected with the disorder have shorten lifespans and overall poor quality of life. Currently, the etiology of schizophrenia is poorly understood however, several lines of evidence suggest a convergence of genetic abnormalities and environmental stresses that affect brain maturation during different states of development. Among the many clinical traits of schizophrenia are cognitive impairments such as deficits in attention, executive function and working memory, traits which suggest dysfunction of the prefrontal cortex. Recent studies in humans have demonstrated a correlation between increased levels of C4 and the risk of developing schizophrenia. Therefore, this study tested how increased expression of C4 alters microcircuits in the prefrontal cortex. Developmental overexpression of C4 resulted in disruption of dendritic spine density and connectivity in the prefrontal cortex of mice. Thus, these results provide evidence for a link between C4 expression and aberrant circuit wiring in the developing fontal cortex.

3-C-113 *Elevated thalamo-cortical coupling in Parkinson's disease detected with magnetoencephalography*

Robin Cash[1], Ke Zeng[2], Matt Brown[3], Robert Chen[4]

[1]Monash University, [2]University Health Network, [3]California State University, [4]Krembil Brain Institute

It has been proposed there may be pathological hyperconnectivity between deeper structures (Basal Ganglia nuclei) and motor cortical areas in PD. These studies were largely possible only in animal PD models or using invasive deep brain stimulation (DBS) in human to obtain local field potential recordings (LFPs) from deeper structures. Our study was designed to reveal the pathological hyperconnectivity with non-invasive magnetoencephalograhy (MEG) and enable the measurement of thalamo-cortical connectivity in PD patients with a direct comparison to healthy individuals. Resting state MEG was recorded from 19 healthy control subjects and 17 PD patients during on and off medications. Individual MRI data was also recorded for source reconstruction. The Linearly Constrained Minimum Variance (LCMV) beamformer was implemented to reconstruct time series related to the centroids of 116 regions-of-interest (ROIs), derived from the Automated Anatomical Labeling (AAL) atlas. For each dataset, we calculated the phase amplitude coupling (PAC) between thalamus beta activity and primary motor cortex gamma activity. It was found that thalamo-cortical PAC was significantly elevated in the patients off medications compared to on medications and for patients off medications compared to controls. This suggests that elevated thalamo-cortical PAC in PD is detectable with MEG, which may provide a noninvasive biomarker of the parkinsonian state.

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3-C-114 *Differentiating the substantia nigra pars compacta and ventral tegmental area in early-stage Parkinson's disease using quantitative susceptibility mapping*

Erind Alushaj[1], Nicholas Handfield-Jones[1], Adrian Owen[1], Ali Khan[1], Penny MacDonald[1]

[1]University of Western Ontario

The midbrain dopaminergic system plays a major role in the pathology of Parkinsons disease (PD). The degeneration of the substantia nigra pars compacta (SNc) causes motor symptoms while neuronal loss in the ventral tegmental area (VTA) causes non-motor symptoms. Iron accumulation is thought to cause this degeneration. Magnetic resonance imaging (MRI) can localize and quantify this iron based on its magnetic susceptibility. Despite all this knowledge, there are no validated biomarkers of PD, but MRI has great potential for their discovery. Twenty early-stage PD patients and age-matched healthy controls were scanned at 3T and 7T. T1-weighted anatomicals were used for segmenting the midbrain structures (VTA, SNc and SNr) based on the CIT168 probabilistic subcortical atlas (2018). Then using quantitative susceptibility mapping (QSM) and R2* mapping registered to these anatomicals, we segmented the structures and analyzed the average iron content in the SNc, SNr and VTA. Repeated measures analysis of variance of average susceptibility values from QSM revealed significantly higher SNc iron content in early-stage PD patients compared to elderly controls at both field strengths. R2* mapping could only detect this difference at 7T suggesting this method is less sensitive than QSM. No significant group differences in iron content were found in the SNr or the VTA. The increased iron load in the SNc of early-stage PD patients, best detected using QSM, could be the first diagnostic biomarker of PD following validation.

3-C-115 *The role of the Interleukin-1 system in alcohol-induced cortical dysfunction*

Florence Varodayan[1], Amanda Pahng[2], Tony Davis[3], Tali Nadav[1], Michal Bajo[1], Michael Burkart[3], Scott Edwards[2], Amanda Roberts[1], Marisa Roberto[1]

[1]The Scripps Research Institute, [2]Louisiana State University Health Sciences Center, [3]University of California, San Diego

Interleukin-1β (IL-1β) is a key regulator of the brain's response to alcohol. IL-1β is elevated in human alcoholic and ethanol-dependent rodent brains, and its neuroinflammatory response is associated with cognitive deficits in ethanol-dependent rodents. Here we investigated the mechanisms of ethanol-induced neuroadaptation of IL-1 signaling at GABAergic synapses in the prelimbic medial prefrontal cortex, an area responsible for drug-seeking behaviors. We found that IL-1β (50 ng/mL) reduced inhibitory input (i.e. less GABA release) onto prelimbic layer II/III pyramidal neurons in naïve C57BL/6J mice. This effect was sensitive to acute ethanol, as a 10 min

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ethanol pretreatment (44 mM) caused IL-1β to enhance GABA release. Importantly, this IL-1β functional switch required the presence of ethanol in naïve mice, but persisted in alcohol-dependent mice (with no acute ethanol present). These dual effects of IL-1β are mediated by selective recruitment of pro-survival (PI3K/Akt) and pro-inflammatory (MyD88/p38) intracellular cascades, with both acute and chronic alcohol producing a pro-inflammatory bias to increase cortical inhibition. Potential chronic ethanol-induced changes in the expression of IL-1 signaling molecules and these two intracellular cascades are currently being assessed using several molecular biology methods. As the IL-1 receptor antagonist (kineret) is an FDA approved drug, this work underscores its potential for treating the cognitive deficits associated with alcohol use disorders.

3-C-116 *Oxytocin normalizes altered social circuit connectivity in the Cntnap2 knockout mouse*

Katrina Choe[1], Martin Safrin[1], Richard Bethlehem[2], Neil Harris[1], Daniel Geschwind[1]

[1]University of California, Los Angeles, [2]University of Cambridge

Aberrant functional connectivity (FC) is often found in autism spectrum disorders (ASD), notably correlating with the degree of social impairment (Supekar et al., 2013). In our previous work, exogenous administration of oxytocin (OXT) or DREADD activation of paraventricular nuclei (PVN) OXT neurons improves social deficits in mice lacking an ASD risk gene, Cntnap2. Given that OXT can increase circuit signal-to-noise by modulating interneuron function (Owen et al., 2013), we hypothesized that OXT might exert its prosocial effects via rescuing FC alterations. To test this, we used high field (7T) resting-state fMRI to assess the effects of OXT on FC in dexmedetomedine-sedated wild-type (WT) and Cntnap2 KO mice (n=15 each). In KO mice at baseline, we observed significantly lowered mean FC between brain areas with established roles in social behavior (e.g. PVN, nucleus accumbens (NAcc), medial prefrontal cortex), but significantly higher mean FC between these and other areas not typically involved in social functions (e.g. sensory cortices, thalamus; $p<0.001$ vs WT, Monte Carlo test), similar to observations made in individuals with ASD (Rudie et al., 2013). Strikingly, these FC phenotypes were normalized by OXT administration ($p<0.001$). Using both pairwise ROI and independent component analyses, we observed that OXT induces a KO-specific activation of NAcc and connected areas, a result that we confirmed histologically using c-Fos immunostaining. These results suggest that the observed social deficits in KO mice are potentially related to lowered FC between social areas, which can be temporarily normalized by OXT administration. We are currently testing the functional significance of NAcc circuit activation by OXT in social rescue using optogenetic behavior test and fMRI.

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3-C-117 *Beneficial effects of ketogenic and beta-hydroxybutyrate diets on socio-cognitive deficits and glucose metabolism in NMDA receptor deficient mice*

Tatiana Lipina[1], Laura Pepera[1], Amy Ramsey[1]

[1]University of Toronto

Grin1 knockdown (Grin1KD) mice have a reduction in functional NMDA receptors, which causes behavioural phenotypes. Previous studies found deficient glucose uptake in the brains of Grin1KD mice. We hypothesize that Grin1KD mice could benefit from a shift in their brain metabolism from glucose to fatty acid utilization as an alternative source of energy. The current study asked whether maintenance on KD or BHB would prevent Grin1KD behavioural and metabolic impairments. Behavioural analysis revealed that KD elicits its effects in age-dependent manner given to Grin1KD mice and their wildtype (WT) littermates from 3 to 12 weeks of age. Significant improvements in working memory and hyperactivity were detected after 5 weeks of maintenance on KD, but 9 weeks of KD corrected deficient social behavior, sensorimotor gating and acoustic startle response in Grin1KD mice. To determine whether the beneficial effects of KD could be replicated with oral BHB supplementation, we also tested behavioral effects of BHB [60 mg/kg; added in water bottles]. In parallel, we found that Grin1KD mice fail to elevate blood glucose with exercise to exhaustion on the treadmill, whereas WT animals showed significant raise of glucose after exercise. To directly probe brain bioenergetics, mitochondrial function was assessed by MitoSox Red in cortical and striatal slices from experimental mice. Altogether, our results demonstrate the ability of mild therapies such as a KD or BHB-enriched water to improve metabolic and behavioral phenotypes of Grin1KD mice. Further studies are needed to determine mitochondria-dependent key molecular players that control bioenergetics and can be used as potentially new targets for the treatment of neurodevelopmental disorders caused by NMDA receptor deficiency.

3-C-118 *A mechanism for spatially and temporally varying neuronal responses to static, spatially varying stimuli*

Jason Pina[1], Bard Ermentrout[1]

[1]York University

In pattern-sensitive epilepsy and with so-called uncomfortable images, visual stimuli with dominant components within a narrow band of spatial frequencies have been shown to induce temporally varying neural responses in EEG and MEG recordings. However, the mechanism for this strongly sensitive oscillatory response to certain spatial frequencies in populations of neutrons is unknown. We are therefore motivated to find such spatiotemporal resonance within an analytically tractable framework, thereby furnishing us with a potential mechanism. Mean-field descriptions of neurons known as neural fields have captured many experimentally observed patterns, such as waves in

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cortex and allow us to employ methods from dynamical systems to analyze their behaviors, including numerical bifurcation analysis and perturbation theory. Using a spatially extended neural field model, we captured the desired spatial resonance by choosing parameters such that the model maintains a spatially uniform baseline steady state with no stimulus, but bifurcates to temporally and spatially periodic patterns with stimuli that are near a critical spatial frequency. We are further able to numerically and analytically characterize the onset of the pattern-forming instability as a function of certain network parameters. Our results suggest that different parameter values involving, for example, the connection strengths between neurons could cause neuronal networks to exhibit a natural sensitivity to particular spatial frequencies, as observed with aversive images and in pattern-sensitive epilepsy.

D - Sensory and motor systems

3-D-119 *Alpha-lipoic acid mitigates toxic-induced demyelination in the corpus callosum by lessening of oxidative stress and stimulation of polydendrocytes proliferation*

Mehdi Mehdizadeh[1]

[1]Cellular and Molecular Research Center, Faculty of Medicine, Iran University of Medical Sciences

Multiple Sclerosis (MS), is a disease that degenerates myelin in central nervous system (CNS). Reactive oxygen species (ROSs) are toxic metabolites, and accumulating data indicate that ROSs-mediated apoptosis of oligodendrocytes (OLGs) plays a major role in the pathogenesis of MS under oxidative stress conditions. In this study, we investigated the role of endogenous antioxidant alpha-lipoic acid (ALA) as ROSs scavenger in the OLGs loss and myelin degeneration during cuprizone (cup)-induced demyelination in the experimental model of MS. Our results have shown that ALA treatment significantly increased population of mature OLGs (MOG+ cells), as well as decreased oxidative stress (ROSs, COX-2 and PGE2) and apoptosis mediators (caspase-3 and Bax/Bcl2 ratio) in corpus callosum (CC). Surprisingly, ALA significantly stimulates population of NG2 chondroitin sulfate proteoglycan positive glia (NG2+ cells or polydendrocytes), from week 4 afterward. Accordingly ALA could prevents apoptosis, delays demyelination and recruits OLGs survival and regeneration mechanisms in CC. We conclude that ALA has protective effects against toxic demyelination via reduction of redox signaling, and alleviation of polydendrocytes vulnerability to excitotoxic challenge.

3-D-120 *Cortical adaptation to limb effector constraints regarding affordance motor action priming*

Stevie Foglia[1], Kumar Somasundram[1], Jim Lyons[1]

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[1]McMaster University

Object grasping is a specialized behavior, due to the coordination of specific grasping configurations of the hand. The information from objects conveys meaning associated with the potential action possibilities afforded by the object to the system, which is integrated by the anterior intraparietal area (AIP) and ventral premotor area (PMv) of the ventro-dorsal stream. Questions remain as to the extent to which the visuomotor system can immediately adapt integration of affordance information to reflect differing parameters the system may encounter (e.g., limb constraint). In this study participants were presented images of a 3-dimesional pole that varied in orientation. On day 1, participants made responses by raising their arm towards the object as if they were to grasp it. On Day 2, one of the arms was constrained using a sling and responses were made with the free arm. Electromyography (EMG) of the anterior deltoid of each shoulder was recorded to determine premotor reaction time. Preliminary results suggest that affordance information from graspable objects prime motor interactions with that object. These early results suggest this information reflects the primed activation of the effector that would be most optimal to grasp the object as to limit excessive wrist deviation. When one arm is constrained however, perceptual information is integrated exclusively toward the unaffected limb. Thus, the action opportunities graspable objects afford are equally considered by the system, irrespective of optimality, as only one effector is capable of producing grasping actions.

3-D-121 *Fine orientation processing in the tactile periphery*

Vaishnavi Sukumar[1], J Andrew Pruszynski[1]

[1]University of Western Ontario

First-order tactile neurons signal information about touched objects. We have recently shown that these neurons extract the geometric features such as edge orientation. Here, we probed the robustness and fidelity of this edge orientation processing for finely spaced edges presented over a wide range of stimulation speeds. We recorded from 56 human first-order tactile neurons - 32 fast-adapting Type-1 (FA-1) innervating Meissner corpuscles and 24 slow-adapting Type-1 (SA-1) innervating Merkel endings. The stimuli were edges embossed on a rotating drum, oriented 5 to 20 degrees relative to the fingertip, presented at 12 speeds from 2.5 to 270 mm/s speeds. Responses of both FA-1 and SA-1 neurons robustly discriminated the edges at slow and medium speeds. Contrary to previous notions about the relative specialization of SA-1 neurons for signaling fine spatial details, we found that FA-1 neurons carried substantially more information about fine differences in edge orientation. Our results suggest that first-order tactile neurons signal fine edge orientations robustly across a broad range of speeds used during normal hand function, and that FA-1 neurons are particularly important for processing finer details of touched objects.

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3-D-122 *Neocortical inhibitory interneuron subtypes display distinct responses to rate and synchrony of spiking activity*

Matthew Tran[1], Luke Prince[1], Dorian Grey[2], Lydia Saad[1], Helen Chasiotis[2], Blake Richards[1]

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

Sensory circuits in the neocortex can carry information using both the rate and the synchrony of spikes in populations of neurons. However, it is unknown whether distinct subtypes of neurons in the cortical microcircuit are more sensitive to information carried by rate versus synchrony codes. Here, we address this question using patterned optical stimulation in slices of barrel cortex from transgenic mouse lines labelling distinct interneuron populations: fast-spiking parvalbumin positive (PV+) and somatostatin positive (SST+) interneurons. We use optical stimulation of channelrhodopsin-2 (ChR2) expressing excitatory neurons in layer 2/3 in order to encode a random 1-bit signal in either the rate or synchrony of activity. We then examine the mutual information between this 1-bit signal and the voltage and spiking responses in PV+ and SST+ interneurons. We find that for a rate encoding, SST+ interneurons carry more information than either PV+ or negative controls, but only after several milliseconds. In contrast, for a synchrony encoding, PV+ interneurons carry more information in the first 5 milliseconds, while both interneuron subtypes carry more information than negative controls in their later response. These data demonstrate that inhibitory interneuron subtypes in the neocortex have distinct responses to information carried by rates of activation versus synchrony of activation.

3-D-123 *Decoding eye-head-hand coordination in primate premotor cortex during visually guided reaches.*

Veronica Nacher[1], Harbandhan Arora[1], Vishal Bharmauria[1], Xiaogang Yan[1], Saihong Sun[1], Hongying Wang[1], John Douglas Crawford[1]

[1]York University

In natural conditions, reaching involves a coordinated sequence of gaze, head, and arm movements toward a visual stimulus. Several studies have examined eye-head-hand coordination in the human, but the underlying neural mechanisms, especially those controlling head motion, have not been studied. To this aim, two monkeys were trained in a reaching paradigm that allowed unencumbered head motion and reaching in depth. Gaze, head and motion were recorded using search coil and touch screen technology, respectively. Animals touched one of three central LEDs at waist level while maintaining gaze on a central fixation dot and were then rewarded if they touched a target appearing at one of 15 locations in a 40° x 20° (visual angle) array. Simultaneously, extracellular single unit activity was mapped across an area putatively including

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frontal eye fields, dorsal and ventral premotor cortex (PMv). Behavioural analysis showed the expected gaze-head-reach sequence, with enhanced gaze accuracy and increased head movement during and after the gaze shift, compared with no-reach controls. Preliminary neurophysiological analysis (in PMv so far) showed an assortment of stimulus, gaze, pre-reach, reach-related responses. A spatial model-fitting analysis suggests that the visual response best encoded the target relative to the eye, whereas the gaze and hand onset responses showed a tendency towards coding the accompanying head motion in space coordinates. A more complete analysis will aim to describe the complete coding and distribution of gaze, head, and reach signals in this region.

3-D-124 *Classifying interneurons based upon responses to top-down feedback in the barrel cortex*

Lydia Saad[1], Dorian Grey[2], Helen Chasiotis[2], Matthew Tran[1], Blake Richards[1]

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

Traditional methods of neuron classification often utilize specific genetic markers in conjunction with electrophysiological and morphological data to create discrete cell-type categories. For example, much of the research dedicated towards interneuron diversity in the neocortex has largely focused on parvalbumin positive (PV+), somatostatin positive (SST+) and vasoactive intestinal peptide positive (VIP+) cells because of their distinct genetic, morphological and electrophysiological characteristics. However, recent work using single cell RNA sequencing suggests there is greater interneuron diversity than previously realized. Given that the neocortex contains many feedback and feedforward connections, a useful classification system should also provide insight into how these neurons may be connected to different regions, rather than simply describe broad cellular characteristics. For instance, while the local connections of PV+ and SST+ cells are well known, there is little work examining the responses of these neurons to inputs from higher order brain regions. Here, we combine immunohistochemistry, electrophysiology, and optogenetics to study the cellular responses to top-down feedback as one potential part of cellular diversity. We hypothesize that distinct PV+ and SST+ interneurons may respond differently to these inputs. These results would imply that a diversity of functional subclasses may exist within these broader interneuron classes and suggests that a more multifaceted strategy may be needed to better understand the functional importance of different cell types.

3-D-125 *Maturation of grasping through increased presynaptic inhibition of sensory feedback to di3 interneurons*

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Nicolas Lalonde[1], Carl Farah[1], Tuan Bui[1]

[1]University of Ottawa

In neonates, grasping is reflexive and hand closing is predominantly elicited by sensory feedback in the hand. During development motor circuits are modified such that supraspinal influences direct integration of descending commands, sensory feedback, and spinal circuitry to elicit skilled grasping. Changes in motor circuit organization which promote motor maturation are not well described. We propose that dI3 INs, a population of spinal interneurons characterized by the expression of Islet 1, form circuits that are ideal for describing mechanisms of sensorimotor integration. When dI3 INs are silenced by Isl1 driven excision of glutamatergic transmission, the regulation of grip strength is lost and neonatal reflex grasping in absent. Normally, the palmar grasp reflex (PGR) is present early after birth and its appearance decays until about 21 days of age at which point neural circuits are sufficiently mature to fully mask the PGR. We hypothesize that PGR masking during development may reflect maturation of dI3 IN circuitry necessary to acquire skilled gripping. We aimed to follow the development of sensory and cortical inputs to dI3 INs during the loss of neonate PGR to assess the maturation of dI3 IN connectivity and its potential for motor control refinement. Immunohistochemically labeled sensory, corticospinal and presynaptic contacts at various developmental time-points in Isl1-Cre; Rosa26-YFP mice reveals increased presynaptic inhibition of sensory inputs to di3 INs from p7 to p21. We thus posit its importance in the acquisition of controlled grip during development.

3-D-126 *GABA concentration in the auditory cortex and aging-related decline in speech-in-noise understanding*

Simon Dobri[1], Bernhard Ross[1]

[1]University of Toronto, Rotman Research Institute

For people of an advanced age, general hearing loss is a major cause of difficulty understanding speech in noise. However, aging-related deficits in central auditory processing also contribute significantly to problems with speech-in-noise understanding by degrading the listener's ability to separate speech sounds from background noise. Recent research suggests that a reduction in the concentration of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) alters the dynamics of cortical gamma oscillations involved in sensory perception. The concentration of GABA in the auditory cortex is lower in older listeners compared to younger listeners, and for those suffering from presbycusis compared to older listeners with normal hearing. Our study aims to expand on these observations by relating GABA concentration to measures of speech-in-noise understanding. We recorded the GABA concentration in both the left and right auditory cortex for a group of healthy young adults and a group of healthy older adults using MEGA-PRESS spectroscopy. Pre-processing and metabolite quantification were performed using an in-house

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toolkit. We determined the pure tone hearing threshold for individuals in both groups, and administered the QuickSIN and Speech Perception In Noise (SPIN) tests to individuals in the older group. Our results indicate a relationship between age and GABA concentration, and between GABA concentration and both pure tone hearing threshold and speech-in-noise comprehension. Our results also suggest hemispheric asymmetry in some of these relationships.

3-D-127 *The effect of visual conditioning on cortical map plasticity: a wide-field calcium imaging study*

Guillaume Laliberté[1], Elvire Vaucher[1]

[1]Université de Montréal - Laboratoire Vaucher

Visual conditioning can refine the response of neurons in the visual cortex and higher visual and cognitive processing of a presented stimulus. The objective of this project is to determine the effect of daily visual conditioning on the distribution and amplitude of cortical responses. For this, we use wide-field calcium imaging in awake mice, allowing us to define the functional organization and plasticity of visual areas. GCaMP6s mice, are used to longitudinally measure spontaneous activity at rest, as well as the cortical responses to a sinusoidal grating with different orientation, space frequency and orientation are recorded to establish response maps and tuning curves. The baseline function of the cortex and the modification of the responses are studied during the monocular conditioning, consisting of a specific grating presented daily over a week. The variations in intensity and activation specificity for the conditioned stimuli are compared with a non-conditioned stimulus. The cortical activation curves show a greater sensitivity of response to stimuli having horizontal or vertical gratings than for oblique gratings at low spatial. However, this trend does not occur with high spatial frequencies. Conditioning at a stimulus results in greater activation of the primary visual cortex and some extra-striate visual areas, as well as a higher ipsilateral cortical response after the presentation of the conditioned stimuli. In conclusion, the results demonstrate that visual conditioning would allow for plasticity and consolidation of higher visual pathways.

3-D-128 *Gain scaling adaptation in vestibular thalamus*

Graham McAllister[1], Jerome Carriot[1], Jessica Brooks[1], Hamed Hooshangnejad[2], Kathleen Cullen[2], Maurice Chacron[1]

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

Growing evidence shows that neural sensory systems actively adapt their responses to efficiently encode non-stationary natural stimuli. Since vestibular stimuli in natural contexts are highly non-

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stationary, and given that thalamus vestibular responses are highly nonlinear, we investigated whether gain scaling adaptation also occurs in vestibular thalamus neurons. We recorded extracellular single-unit neural responses in the ventral posterior lateral thalamus of 2 rhesus macaque monkeys, during sinusoidal horizontal head rotation with steps (10 to 40 deg/s) or gradual increases (10 to 100 deg/s) in peak velocity. We calculated the time-dependent neural gain and its relationship to the stimulus amplitude (i.e. how changes in peak amplitude affect gain over time). We found that the neural response to amplitude steps was strongly nonlinear, and the neural gain adapted significantly following the amplitude step. Gain scaled inversely with peak amplitude; this scaling consisted of an initial rapid component followed by a gradual adaptive decrease over 2-5 seconds. We found that the neural response to smoothly increased peak amplitude was also nonlinear, with a three-fold reduction in gain. The gain decreased exponentially with increasing peak amplitude, with a greater time constant at higher rotation frequencies. In conclusion, we have found that adaptive gain scaling is a novel mechanism by which the posterior ascending vestibular pathway processes self-motion to ensure reliable perception in varying sensory contexts.

3-D-129 *Thalamus coding strategies for representing natural self-motion*

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

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

Self-motion is sensed by the vestibular system, contributing to automatic reflexes and spatial perception. However, the coding strategies used by the vestibular system to process natural self-motion is largely unknown because artificial (e.g., sinusoidal) stimuli have been typically used to date. It is commonly assumed that, through evolutionary and developmental processes, sensory neurons are adapted to the statistical properties of the stimuli to which they are exposed. Here, we investigated how neurons within the ventral posterolateral (VPL) nucleus of Thalamus respond to natural motion. These neurons receive direct projections from vestibular nuclei (VN) neurons and provide a gateway for sensory information to reach cortical areas and give rise to perception. While we have shown that VN neurons optimally encode natural motion through temporal whitening, thereby maximizing information transmission, our results show this is not the case for VPL neurons. Rather, the response power spectra of VPL neurons decayed with increasing frequency, indicating that they do not perform temporal whitening. To explain this surprising result, we built a model that incorporates the response properties of VN neurons. Our model reproduced the experimental data and predicted that it is the large variability displayed by VN neurons that is detrimental to information transmission at high frequencies. We predict this coding strategy is advantageous to extract low frequency features relevant for perception. Our results have important implications for understanding how self-motion is perceived.

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3-D-130 *Re-evaluation of luminance evoked pupil response dynamics*

Jonathan Coutinho[1], Douglas Munoz[1], Gunnar Blohm[2]

[1]Queen's University, [2]Center for Neuroscience Studies, Queen's University

Pupil responses are commonly used in clinical assessments and as a proxy for cognitive processes in psychological research. Making accurate inferences from these measures requires precise knowledge of the underlying system dynamics. However, the precise system dynamics of pupillary responses are poorly quantified. As a result, there is a lack of consistency in the selection of pupil metrics and the preprocessing and analysis of pupil response data across the literature. Meanwhile, existing pupil models rely on simplistic assumptions of underlying control signals, resulting in poor generalizability. Thus, better quantification of the control system and neuromuscular properties of pupil response dynamics would substantially advance the utility of pupillometry in cognitive and clinical neuroscience research. Here we quantify pupil responses to the simplest possible sensory stimulus, i.e. large-field changes in luminance, randomly selected between 1 and 49 cd/m2. We found large variability in baseline pupil sizes within and between subjects. Nevertheless, we found a linear relationship between average changes in pupil size and the difference in log-luminance during a luminance transition. Furthermore, we found covariance between the amplitude and peak velocity of pupil responses suggestive of a "main sequence" in the pupil control. We quantified aspects of dynamic pupil responses, including saturating non-linearities and asymmetries between constriction and dilation dynamics. The quantification of these responses serves as a foundation for future pupil modelling.

3-D-131 *The functional role of enhancing the activity and survival of progenitor cells during stroke recovery*

Sebastien Denize[1], Maheen Ceizar[1], Yingben Xue[1], Diane Lagace[1]

[1]University of Ottawa

There is a significant increase in the number of dividing progenitor cells (PCs) following a stroke that ectopically migrate to the site of injury. The functional significance of these cells is controversial, because most of the cells that migrate are unable to survive and if the cells do survive, whether they receive activation remains unknown. This study tests if enhancing the survival of the PCs, and/or optogenetic stimulation of the PCs, is sufficient to improve stroke recovery using inducible BAX (iBAX) transgenic mouse models. Specifically, one week after photothrombosis-induced stroke, tamoxifen (TAM) treatment allows for: 1) the removal of Bax and expression of YFP in the Baxf/fxNestinCreERT2xRosa-YFP (iBAX-YFP) mice; or 2) removal of Bax and expression of channelrhodopsin (CHR2-YFP) in the Baxf/fxNestinCreERT2xChR2-YFP (iBAX-

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CHR2) transgenic mice; in all the nestin-expressing PCs and their progeny. In the iBAX-YFP mice, removal of Bax significantly increased the number of PCs and the majority of the cells had a neuronal phenotype, in the absence of impacting behavioral recovery. In the iBAX-CHR2 mice, daily optogenetic stimulation for 5 weeks in pilot studies, suggests stimulation may improve behavioral recovery. These results have clinical implications in helping to elucidate the beneficial effects of non-invasive brain stimulation, which is being tested in stroke recovery.

3-D-132 *Neural population level noise correlations across three parallel topographic maps in the electrosensory system of Apteronotus leptorhynchus during prey localization*

Myriah Haggard[1], Maurice Chacron[1]

[1]McGill University

Neural population coding is an important component of systems neuroscience. Trial-to-trial variability however is non-negligible in population signals, particularly when the noise structure is correlated between neurons which can affect the encoded information. Previous studies showed that local network circuitry impacts the structure of shared variability in primary visual cortex and that noise correlation structure is stimulus-dependent in direction-selective retinal ganglion cells. This study will investigate the influence of noise correlations on spatial object localization in terms of local circuitry and stimulus-dependence. Object localization is crucial to prey capture in the weakly electric fish, Apteronotus leptorhynchus. The electrosensory system of this animal uses three topographic maps, all of which receive identical cutaneous electrosensory inputs but, due in part to local circuitry causing differential receptor field (RF) center-surround ratios and overlap, each map processes the input differently. Previous work showed that despite this, baseline noise correlations are consistent across the maps. This must now be tested for stimulus-dependence. To this end, prey-mimic stimuli will be played along the length of the fish while recording from correlated neurons in the three maps, allowing spatial mapping of the RFs and the stimulus-dependent noise correlation structure. The results of this study will elucidate how network properties affect noise correlations and therefore population encoding, which is generalizable to visual, auditory and somatosensory systems.

3-D-133 *Reliability and smallest detectable change of short- and long-latency afferent inhibition*

Claudia Turco[1], Angelina Pesevski[1], Paul McNicholas[1], Louis-David Beaulieu[2], Aimee Nelson[1]

[1]McMaster University, [2]Université du Québec à Chicoutimi

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Short-latency afferent inhibition (SAI) and long-latency afferent inhibition (LAI) are well-known transcranial magnetic stimulation (TMS) paradigms used to probe the sensorimotor system. To date, there is a paucity of research examining the reliability of these neurophysiological measures. This information is required to validate the utility of afferent inhibition as a biomarker of neural function. Therefore, the goal of this study was to quantify the absolute and relative reliability, and to obtain the smallest detectable change (SDC) of SAI and LAI using a test-retest paradigm. 30 healthy individuals (20.9 +/- 2.5 years) participated in two sessions (intersession interval of 6.9 +/- 4 days). Reliability was assessed with intraclass correlation coefficients (ICC), standard error of measurement (SEMeas), and SDC. The results show that LAI by digital nerve stimulation revealed moderate relative reliability via the ICC (0.75, 95% CI 0.46-0.88). The remaining measures had low ICCs with large confidence intervals. The SEMeas indicated a large amount of measurement error in all measures. The SDC was large at the individual level, but significantly reduced for the group-level analyses. Our results indicate LAI by digit stimulation has moderate reliability differentiating between individuals within a sample. Further, SAI and LAI are reliable for exposing differences in the group-averaged data obtained on two occasions but should not be used to assess differences within a participant.

3-D-134 *Population coding in central vestibular pathways during naturalistic stimuli*

Mohammad Mohammadi[1], Mohammad Mohammadi[1], Isabelle Mackrous[1], Jerome Carriot[1], Kathleen Cullen[2], Maurice Chacron[1]

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

Population coding in the vestibular system is understudied as mostly single unit recordings have been used. (Liu et al., 2013) performed multiunit recordings and measured correlations in VN using artificial (e.g. sinusoidal) stimuli. Unlike artificial stimuli, naturalistic stimuli have larger amplitudes and a wider range of temporal frequencies which theoretically impact correlations and coding. Accordingly, we measured the correlations in Vestibular Nuclei (VN) and Ventral Posterolateral (VPL) nucleus in the thalamus by recordings from pairs of vestibular neurons during naturalistic stimuli. First, we quantified noise correlations during baseline activity, artificial as well as naturalistic stimuli. We found that pairs exhibited significant noise correlations during baseline activity and artificial stimuli, but these reduced greatly during naturalistic stimuli suggesting that neural populations in VN implement optimized coding via redundancy reduction during naturalistic stimuli. Next, we performed multiunit recordings from VPL during naturalistic stimuli and found that 1) noise correlations decrease significantly in VPL compared to VN, and 2) structure of correlation is fundamentally different from that of VN in that noise and signal correlations have opposite signs so that raw correlations are small. These findings reveal that neural activities become decorrelated in VPL and provide an optimal estimation of sensory input for cortical areas.

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3-D-135 *Coding of saccade targets in primate hippocampus. A comparison with the lateral prefrontal cortex*

Ben Corrigan[1], Roberto Gulli[2], Guillaume Doucet[3], Julio Martinez-Trujillo[1]

[1]University of Western Ontario, [2]Columbia University, [3]Ottawa Hospital Research Institute

Primate vision processing is highly developed, with high acuity at the fovea which requires saccades to explore the visual world. The hippocampus (Hc) has been reported to encode saccade target locations. We set out to investigate presaccadic tuning for saccades in this area, using recordings in area 8A of the lateral prefrontal cortex as a control region. Three macaques (macaca mulatta) performed a cued saccade task, but we took saccades in the intertrial intervals to analyse spontaneous saccades. They also did a learning task in a virtual environment where two different coloured discs were presented, but value was contingent on a separate context so value was decorrelated from position and colour. We recorded 120 single units over 30 sessions from HC of two NHPs with single electrodes. The other NHP had two Utah arrays in area 8A, and we recorded from 520 neurons over four sessions. Screen space was divided into 9 equal sized bins (10° x 8°), and we used a permutation test see if the average firing rate was higher than expected by chance in any bins for spontaneous saccades. We did not find any units tuned to spontaneous saccade targets in the hippocampus. 14% of PFC neurons were tuned to at least one location. In the VR task, saccades were confined to the targets, so comparisons were between the two target locations. We found that 10% of HC neurons had saccade direction selectivity that was not explained by target value or colour. 20% of PFC neurons were tuned to target screen position, regardless of value or colour.

3-D-136 *Postural state modulation of cortical activity associated with balance reactions*

Mark Laylor[1], Paula Polastri[2], Jessy Varghese[1], William McIlroy[1]

[1]University of Waterloo, [2]Sao Paula State University

Gait poses a challenge to the nervous system with simultaneous control of progression and stability. Phasic modulation of stability may explain cortical involvement in gait. We explored state modulation of cortical activity time-locked to the onset of a balance perturbation (N1 response). The study aims to describe cortical excitability through the N1 during lateral weight shifts emulating gait. We hypothesize that N1 peak amplitude will be greater during lateral weight shifts. We also hypothesize that N1 peak amplitude will be greater for perturbations opposite to weight shift direction where participants reach their base of support (BOS) limits faster. Young healthy adults stood on a platform designed to induce unpredictable balance perturbations in 3 stances: equal weight and at least 90% weight lean on the left or right leg. Perturbation direction was randomized and counterbalanced as CONTROL (left/right during equal weight stance), CONGRUENT (same direction as lean) and INCONGRUENT (opposite direction to lean).

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Perturbation amplitude was based on an acceleration threshold to not evoke stepping. Thirty trials of control, congruent, and incongruent were collected. Cortical activity was measured with 32 channel electroencephalography sampled at 1000 Hz. Initial results demonstrate an increase in N1 peak amplitude during incongruent perturbations. Similar modulation of cortical activity may occur during walking where the relationship between posture and BOS limits are constantly changing. Ongoing analysis will focus on the network connectivity underlying this modulation.

3-D-137 *An algorithmic impediment to understanding neural circuits via circuit interrogation*

Venkatakrishnan Ramaswamy[1]

[1]National Centre for Biological Sciences

Neuroscience is witnessing extraordinary progress in experimental techniques, especially at the neural circuit level. In addition to imaging activity of individual neurons (including whole-brain imaging), techniques such as 2-photon optogenetics are affording us the ability to perturb activity of arbitrary subsets of neurons in behaving animals, enabling us to understand how activity of neurons in circuits mechanistically causes behavior. However, to arrive at such a causal understanding, it appears necessary to perform multiple perturbation experiments. It is as yet unclear how many experiments are so needed and how this number scales with the size of the nervous system in question. Here, using techniques from Theoretical Computer Science, we examine how many experiments are needed to obtain such an empirical understanding. It is proved, mathematically, that establishing the most extensive notions of understanding need exponentially-many experiments in the number of neurons, in general, unless a widely-posited hypothesis about computation is false (i.e. unless P=NP). Worse still, the feasible experimental regime -- for most organisms of interest -- is one where the number of experiments one can perform in the lifetime of an individual organism, scales sub-linearly in the number of its neurons. This remarkable gulf between the worst-case and the feasible suggests the existence of a fundamental algorithmic impediment to such an understanding. Determining which notions of understanding are algorithmically tractable thus, becomes an important new endeavor in Neuroscience.

3-D-138 *Genital stimulation facilitates a sexual reward state in male and female mice*

Thanh Phung[1], Firyal Ramzan[2], Ashley Monks[2]

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

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Genital tactile stimulation is seen as a precursor to sexual arousal and is recognized as an initiator of CNS arousal. Previous rodent studies have demonstrated that tactile stimulation of the clitoris is sufficient enough to induce a reward state in female rats. However, it is unknown whether genital tactile stimulation could also induce a hedonic state in male rodents. The present study examined the ability of clitoral and glans penis stimulation to induce a conditioned place preference (CPP). Sexually naïve and gonadally intact C57BL/6 mice were randomly assigned to receive either genital or dorsum stimulation. Stimulation was performed at 1 stroke per second for one minute prior to being placed in one side of a nonbiased CPP box for two minutes. A session of conditioning consisted of 5 rounds of stimulation and place exposure per day. Conditioning sessions alternated with sham sessions in which mice received handling, but no tactile stimulation. Place exposure was for non-preferred side (conditioning) and preferred side (sham). CPP was assessed once all animals had completed 5 conditioning and sham sessions. It was found that all animals subjected to genital stimulation developed a significant CPP, whereas a significant CPP for dorsum stimulation was only developed in male mice. This suggests that despite morphological differences, the clitoris and the glans penis possess a similar role in generating a reward state upon stimulation. Additionally, the development significant CPP in male mice who received dorsum stimulation highlights a sex-difference in tactile reward.

3-D-139 *Saphenous nerve ligation elicits widespread alterations in cortical dynamics*

Donovan Ashby[1], Jeffery LeDue[2], Timothy Murphy[2], Alexander McGirr[1]

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

Chronic neuropathic pain is accompanied by cortical functional reorganization that may contribute to hyperalgesia and dysthesia. Saphenous nerve ligation in mouse is a well-validated animal model of neuropathic pain that produces hyperalgesia circumscribed to the hindlimb. While cortical alterations have be observed in specific regions in various models of neuropathic pain, widespread alterations have been difficult to capture due to limitations in recording activity across a broad cortical expanse. Mesoscale cortical imaging leverages optical sensors of neuronal activity to simultaneously image across a wide expanse of cortex, permitting characterization of large scale networks and their impact on sensory processing. Saphenous nerve ligation or sham was performed in mice, and after 10 days we performed voltage sensitive dye (VSD) imaging using a large bilateral craniotomy. Under light isoflurane anesthesia, we conducted sensory mapping of the affected limb and unaffected locations at multiple stimulus intensities, and acquired spontaneous activity to characterize large scale network reorganization. While the hindlimb primary sensory-evoked response was unaffected, the propagating wave of activity was markedly reduced in ligated mice. We observed widespread alterations in spontaneous cortical dynamics, including power spectra alterations and functional connectivity changes. These results

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reveal widespread cortical changes in response to a localized peripheral insult, with implications for novel circuit level interventions in neuropathic pain and other diseases.

3-D-140 *Investigating delayed motor learning of 16p11.2+/- mouse model of autism via in vivo two-photon imaging*

Xuming Yin[1], Nabil Asraoui[1], Marie-Eve Mathieu[1], Nathaniel Jones[1], Simon Chen[1]

[1]University of Ottawa

The 16p11.2 chromosomal copy number deletion accounts for approximately 1% of autism spectrum disorder (ASD) cases in humans. ASD patients also exhibit motor deficits and clumsiness. However, despite the prevalence of this disorder, the neural pathophysiology underlying these symptoms remains elusive. We trained mice to run on a novel head-fixed running wheel apparatus and found that 16p11.2+/- mice do not show any movement deficits, but exhibit a delay in motor learning compared to the wild-type (WT) mice. Using chronic in vivo two-photon imaging, we found 16p11.2+/- mice exhibit abnormally high spine density in the primary motor cortex (M1) and undergo a delayed process of learning-induced spine reorganization. At the population level, 16p11.2+/- mice show a distinctive neuronal population that is highly clustered and synchronized during running. Surprisingly, this population only exists in initial training sessions but disappears with learning. Lastly, we identified a layer-specific loss of noradrenergic (NA) innervation in the L2/3 of M1 in the 16p11.2+/- mice. Activating NA neurons in the locus coeruleus via DREADDs manipulation rescues the delayed motor learning, as well as the delayed spine reorganization in 16p11.2+/- mice. These results demonstrate, for the first time, a layer-specific loss of NA innervations that is accompanied by deficits in synaptic reorganization, ensemble activity patterns, and delayed motor learning in a mouse model of autism, which can be rescued by NA activation during learning.

3-D-141 *Characterization of the role of dorsal horn calretinin-expressing interneurons to the processing of pain inputs*

Hugues Petitjean[1], Farin B. Bourojeni[2], Deborah Tsao[1], Davidova Albena[1], Susana G. Sotocina[1], Jeffrey S. Mogil[1], Artur Kania[2], Reza Sharif-Naeini[1]

[1]McGill University, [2]Institut de Recherches Cliniques de Montréal

The dorsal horn of the spinal cord (DH) is the first relay centre of somatosensory information originating from the periphery. In the superficial DH laminae I-II, nociceptive information is processed by a complex network of excitatory and inhibitory interneurons whose function and connectivity remain poorly understood. In this study, we examine the role of calretinin-expressing

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interneurons (CR neurons) in the processing of innocuous and noxious sensory inputs. These neurons are mainly located in lamina II, where they receive direct inputs from the central endings of nociceptive fibers and polysynaptic inputs from touch-sensitive Aβ fibers. Their activation by either chemogenetic or optogenetic stimulation produces mechanical allodynia and nocifensive behaviors. Furthermore, we examined the position of CR neurons in the DH circuitry, where they would be ideally positioned to modulate the activity of pain projection neurons in lamina I. In conclusion, we propose a new neuronal pathway in which CR neurons are positioned at the junction between incoming nociceptive and innocuous circuits and ascending pain pathways of the dorsal horn.

E - Homeostatic and neuroendocrine systems

3-E-142 *Neural mechanisms of multiplexed egocentric and allocentric gaze coding in monkey frontal eye fields*

Vishal Bharmauria[1], Amirsaman Sajad[2], Xiaogang Yan[1], Hongying Wang[1], John Douglas Crawford[1]

[1]York University, [2]Vanderbilt University

Behavioral studies in humans have shown that the visual system optimally combines egocentric and allocentric cues for goal-directed movements (Byrne & Crawford 2011; Klinghammer et al., 2016, 2017), but the underlying neural mechanisms are unknown. Based on our fRMI results (Chen et al. 2018), we focused on the monkey frontal eye fields (FEF), which possess visual (V), memory (Me), and motor (M) signals for the cortical gaze output command. In egocentric-only studies, we found that FEF 'V' responses coded target relative to the eye (Te), whereas 'M' responses coded future gaze relative to the eye (Ge) (Sajad et al. 2015, 2016). Here we tested the V, Me, and M response fields (RFs) of 173 FEF neurons in two Rhesus macaques which were trained to make gaze shifts toward remembered visual targets in the presence of a shifted landmark (L) during the memory delay. Behavioral analysis showed that, as in humans, monkey gaze end-points shifted about 1/3 toward the shifted L. Using model-fitting to track coordinate shifts in RFs, we found that the initial V and Me responses mainly encoded Te, but after the shifted L, a transient coding shift toward T'e (virtual T relative to L) was noticed, primarily in neurons with V responses, and a later shift about 1/3 toward T'e (primarily in neurons with M responses). This Allo-shift was coded as a function of the egocentric code (from T to G) in visuomotor (VM) neurons but this was insignificant in motor neurons. These results show that the cortical motor output is influenced by allocentric visual cues and is multiplexed with egocentric codes

3-E-143 *Glucocorticoid regulation of the G-protein Coupled Estrogen Receptor (GPER) protein expression and signalling in immortalized hippocampal neurons*

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Kate Nicholson[1], Ari Mendell[1], Carolyn Creighton[1], Neil MacLusky[1]

[1]University of Guelph

Estrogens exert neuroprotective and neurotrophic effects within the hippocampus, modulating cognitive function. The non-classical G-protein coupled estrogen receptor (GPER) mediates some of the effects of estradiol (E) within the hippocampus. Previous studies have shown that GPER activation and signalling elicit sexually-differentiated effects on anxiety behaviours and cognitive performance in rodents; but that acute behavioural stresses impair E mediated signalling, neurotrophic effects, and memory formation (Frick et al. Eur J Neurosci, 19 (2004) 3026-32). The mechanisms by which stress inhibits E mediated enhancement of cognitive function remain poorly understood. We hypothesized that stress-induced glucocorticoid (GC) release might downregulate GPER-mediated signalling. To test this hypothesis, two novel lines of immortalized murine hippocampal neurons were used. The mHippoE-14s and mHippoE-18s are T-antigen transformed, phenotypically distinct neuronal cell lines that express many neurotransmitter and neurosteroid receptor mRNAs, including high levels of the GC receptor and GPER. Cells were treated with 10nM of the synthetic glucocorticoid dexamethasone (DEX). Changes in GPER protein expression and functional signalling were assessed 10 min, 1h, 10h, 24h, and 48 h later. The female derived mHippoE-14s exhibited reduced GPER expression and functional signalling 24 hours after DEX, compared to vehicle controls. We conclude that stress may impair E mediated neurotrophic and neuroprotective effects on the hippocampus via down-regulation of GPER-mediated responses.

3-E-144 *Time course of surgical stress and the role of testosterone in the post-operative recovery of hippocampal and medial prefrontal cortex dendritic morphology in adult male rats.*

Lauren Isaacs[1], Eric Lawton[1], Ari Mendell[1], Neil MacLusky[1]

[1]University of Guelph

Gonadal and stress hormones can cause profound changes in hippocampal (HC) and medial prefrontal (mPFC) dendritic morphology which may underlie post-stress cognitive deficits. Previously, our laboratory has demonstrated that orchidectomy (ORCH) increases CA3 apical dendritic branching 10-days and 2-month after surgery compared to sham-operated rats. At 10-days, sham-operated rats have truncation of CA3 apical dendrites while testosterone (T) replacement partially restores CA3 branching. However, the time course following surgical stress and the roles of glucocorticoids (GC) and T remain unclear. We determined the time-course of stress and GC at 1-, 3- and 10-days. Unstressed rats treated with dexamethasone had significantly truncated CA3 apical dendrites 3-days following treatment. To determine the role of T in the recovery of dendritic morphology, rats were either ORCH, ORCH+T replaced, sham-operated or

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kept intact, then sacrificed 1-month and 2-months after surgery. At 1-month, ORCH rats had similar CA3 apical dendritic branching seen at 10-days. While ORCH+T and intact rats had comparable CA3 apical branching, the sham-operated animals had reduced CA3 apical branching. By 2-months, sham-operated rats displayed complete recovery of CA3 apical dendrites. No changes were found in CA1 branching or HC dendritic spine density, in any treatment group. Our results suggest that stress rapidly induces CA3 dendritic remodelling, an effect mediated at least in part by GC action which is modulated during surgical recovery by T.

3-E-145 *Immunohistochemical analysis and atlas mapping of hypothalamic neurons that coexpress tyrosine hydroxylase and the vesicular GABA transporter.*

Kayla Schumacker[1], Rebecca Butler[1], Kenichiro Negishi[2], Mikayla Payant[1], Gabor Wittman[3], Arshad Khan[2], Melissa Chee[1]

[1]Carleton University, [2]University of Texas at El Paso, [3]Tufts Medical School

Catecholamines, which includes dopamine, noradrenaline, and adrenaline, are a major group of biogenic amine neurotransmitters that share properties of neuropeptides and neurotransmitters. Neuropeptide neurons in the hypothalamus typically coexpress with a neurotransmitter like GABA or glutamate. To determine if catecholamine neurons coexpress GABA or glutamate, we first generated transgenic mice to label neurons expressing the vesicular GABA (vGAT) or glutamate transporter (vGLUT2), respectively, with a green fluorescent protein (EGFP). We then determined if vGAT-EGFP or vGLUT2-EGFP neurons coexpress tyrosine hydroxylase (TH), an enzyme required for catecholamine synthesis. Interestingly, hypothalamic TH neurons may coexpress with vGAT but not vGLUT2. We performed Nissl-based parcellations throughout the hypothalamus to systematically map the distribution of TH+vGAT neurons onto coronal atlas plates from the Allen Brain Atlas. This revealed a striking pattern of TH+vGAT colocalization in the zona incerta (ZI). While the ZI spans 2.33 mm along the rostrocaudal axis, TH is only expressed across a 100 µm section through the hypothalamus and 100% of these TH neurons coexpress vGAT. Neurochemical characterization of ZI TH neurons show that they are immunoreactive for dopamine but not dopamine beta hydroxylase, thus their specific catecholamine identity is dopamine, not noradrenaline or adrenaline. These findings suggest that the functional role of ZI neurons, such as in binge eating or sleep regulation, may require the release of dopamine and/or GABA.

3-E-146 *Exposure to the synthetic glucocorticoid dexamethasone downregulates DUSP6 and alters expression of neurological disorder-related genes*

Emily Craig[1], Kate Nicholson[1], Neil MacLusky[1]

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[1]University of Guelph

Evidence for involvement of alterations in gene expression in neurological disease has mounted in recent years, the expression of many genes of interest being directly or indirectly affected by stress. In this study, we determined the effects of the synthetic glucocorticoid dexamethasone (DEX) on expression of genes associated with neurological disease, including FK506 binding protein 51 (FKBP5), Dual Specificity Phosphatase 6 (DUSP6), and the proteins which regulate their action, in a cell culture model. Two T-antigen immortalized mouse embryonic hippocampal cell lines (mHippoE14, female-derived; and mHippoE18, male-derived) were utilized. Cells were treated with 10 nM DEX, and ribonucleic acid (RNA) was collected 6, 12, and 24 h post-treatment to assess the effects. DEX increased expression of FKBP5 in both cell lines at 6 hours, with increasing expression sustained at 24 hours in the mHippoE18 cell line only. Similarly, DEX-induced downregulation of DUSP6 was resolved much more rapidly in the mHippoE14 cells, possibly reflecting the previously-reported sex difference in stress regulation of this gene (Labonte et al Nat Med, 23 (2017) 1102-1111). Expression of FKBP5 and MKP3 have been associated with multiple neurological disorders, including major depressive disorder, bipolar disorder, and schizophrenia. Sex differences in neurological disorders may this, in part, be attributable to sex differences in the stress responsiveness of genes that contribute to disease susceptibility. Acknowledgements: Supported by NSERC and the Ontario Veterinary College.

3-E-147 *Prostaglandin E2 activates corticotropin releasing hormone neurons in the paraventricular nucleus of the hypothalamus.*

Hiroyuki Igarashi[1], Eric Kuebler[2], Julio Martinez-Trujillo[1], Wataru Inoue[1]

[1]University of Western Ontario, [2]Robarts Research Institute

Inflammation activates the hypothalamic-pituitary-adrenal (HPA) axis, and the ensuing release of anti-inflammatory glucocorticoids provide critical negative feedback onto the immune system. An inflammatory mediator prostaglandin E2 (PGE2) is a key intermediate for this immune-to-brain signalling driving the HPA axis activation. We recently showed that PGE2 potently inhibits the release of GABA onto the output neuroendocrine neurons of the HPA axis [corticotropin releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN)]. This suggests that PGE2 permits the excitation of PVN-CRH neurons via a removal of GABA-mediated inhibition. However, it remains unclear how PGE2 increases the activities of PVN-CRH neurons. Here, we examined PVN-CRH neurons' response to PGE2 using Ca2+ imaging in acute brain slices. We expressed a genetic Ca2+ indicator GCaMP6s in PVN-CRH neurons by injecting cre-dependent AAV9 expression vector in CRH-ires-cre mice. Two photon real-time imaging revealed that bath application of PGE2 triggered robust, oscillating Ca2+ elevations in a subpopulation of PVN-CRH neurons. These results support excitatory effects of PGE2 on PVN-CRH neurons and also revealed heterogeneity of PVN-CRH neurons in their responsiveness to PGE2.

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3-E-148 *GHSR Signaling in the DMH and its Effects on Energy Homeostasis*

Lindsay Hyland[1], Stephanie DeSante[1], Alex Wiseman[1], Su-Bin Park[1], Alexander Edwards[1], Yosra Abdelaziz[1], Barbara Woodside[2], Alfonso Abizaid[1]

[1]Carleton University, [2]Concordia University

Ghrelin elevates food intake and adiposity through its actions on the GHSR. The GHSR is highly expressed in the dorsomedial hypothalamic nucleus (DMH), a region important for thermogenesis, food intake, and the generation of the stress response. Nevertheless, the effects of ghrelin on the DMH remain to be determined. In experiment 1, we examined the effects of chronic ghrelin signalling stimulation or blockade in the DMH (AP 1.55mm, ML 0.25mm, and DV 5.25 mm) on metabolic parameters (i.e. food intake, body weight, energy expenditure and glucose clearance) in male C57BL/J6 mice using osmotic minipumps attached to cannuli and filled with either saline, ghrelin, or a GHSR antagonist. Because ghrelin is elevated following chronic exposure to stress, we conducted a second experiment in which mice were exposed to chronic social defeat daily for a period of 10 days while receiving chronic intra DMH infusions of saline or a GHSR receptor antagonist, and compared to non-stressed mice given the same intra-DMH treatments. We then compared metabolic outcomes and responses in anxiety measures like the social interaction test. Finally, in experiment 3, anaesthetized mice were given an acute intra-DMH infusion of either saline, ghrelin, or pre-treated with a GHSR antagonist followed by ghrelin, and were monitored for changes in core body temperature and blood glucose levels for 2 hours post-infusion. Our results show that chronic infusions of ghrelin into the DMH affects body weight and fat accumulation, while acute infusions affect blood glucose.

3-E-149 *Fear and anxiety in the hypothalamus*

Tamás Füzesi[1], David Rosenegger[1], Nuria Daviu[1], Neilen Rasiah[1], Govind Peringod[1], Taylor Chomiak[1], Leonardo Molina[1], Grant Gordon[2], Jaideep Bains[1]

[1]Hotchkiss Brain Institute, [2]University of Calgary

It is well established that corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) control the endocrine response to stress. Recent work indicates that PVN CRH neurons also control specific stress-related behaviors that are independent of hormone release. Precisely how these neurons encode both rapid behavior and slow hormone release is not known. Here, we used in vivo single fibre photometry to assess real-time calcium changes in PVN CRH neurons in freely behaving mice. We injected an adeno-associated virus containing a Cre-dependent GCaMP6s construct into the PVN of a CRH-Cre transgenic mouse. Two weeks later, an optical fiber was implanted directly above the PVN.

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Experiments began after one week of recovery and handling. We examined PVN CRH activity in a number of scenarios. Introduction of the animal to a novel environment elicited a sustained elevation in the GCaMP signal. Repeated exposure (4 days) to the same environment did not alter the amplitude of this persistent increase. In response to footshock, CRH neurons showed a rapid, but transient increase in Ca2+. Finally, handling itself also induced an increase in Ca2+ that was similar in magnitude to that observed during footshock. The Ca2+ response remained unchanged by repeated handling sessions. These observations indicate that PVN CRH neurons show distinct activity profiles that reflect the duration and intensity of the stressor.

F - Cognition and behavior

3-F-150 *Cuticular hydrocarbons confer desiccation resistance in D. melanogaster*

Kamar Nayal[1], Joshua Krupp[1], Amy Wong[1], Jocelyn Millar[2], Joel Levine[1]

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

Terrestrial insects are vulnerable to desiccation and maintain the water balance necessary for survival by limiting water loss due to transpiration across the cuticle. The epicuticle, a layer of cuticular hydrocarbon compounds (CHCs) on the outer surface of the insect cuticle, is hypothesized to be integral to preventing water loss, however direct evidence demonstrating the capacity of CHCs to protect against desiccation is lacking. Using Drosophila melanogaster we demonstrate that both the oenocytes and the CHCs produced by these cells are critically important for survival under desiccative conditions. Topical application fly-derived CHC extract or synthetic CHC substitutes to flies lacking oenocytes (and hence endogenous CHCs) demonstrated that both straight-chain alkane and methyl-branched alkane compounds contribute to desiccation resistance but that the native mix of the different classes of compounds is required for maximal protection. Additionally, we show that both mating status and developmental temperature influence desiccation resistance. Prior mating increased desiccation resistance through the direct transfer of CHCs between sexual partners, as well as through a female-specific response to a male-derived factor transferred during copulation. Together, our results demonstrate that desiccation resistance is an adaptive life-history trait dependent upon CHCs and influenced by prior social interactions and environmental conditions.

3-F-151 *Failure of NMDA receptor restoration to serotonin and dopamine cells to improve schizophrenia-like behaviour of GluN1KD mice*

Katheron Intson[1], Maliha Zaman[1], Ali Salahpour[1], Amy Ramsey[1]

[1]University of Toronto

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Despite convincing evidence for the glutamate hypotheses of schizophrenia, gold-standard therapies act via dual partial or transient antagonism of the dopamine and serotonin receptors. Consistently, our mouse model expressing <10% functional glutamatergic NDMA receptors (GluN1KD mice) displays behaviour consistent with schizophrenia; its phenotype is also ameliorated by atypical antipsychotics. Recently, we developed a Cre-inducible-rescue GluN1KD mouse, allowing for cell-population-specific restoration of functional NDMA receptors. We asked whether restoring NMDA receptors within DAT-containing (i.e., dopaminergic) or Pet-1-containing (i.e., serotonergic) cell populations would improve cognitive deficits seen in GluN1KD mice. Despite apparent recovery of NMDA receptors to these areas (visualized using RNAScope in-situ hybridization), we did not see an improvement to the phenotypes of GluN1KD mice in behavioral assays. In fact, female mice with NMDA receptors restored to Pet-1-containing cells had significantly worse locomotor phenotypes and a higher number of seizures. We conclude that rescue of the serotonin and dopamine cell populations is insufficient for improving symptoms consistent with schizophrenia in our mouse model.

3-F-152 *The memories that linger: the effect of opiate withdrawal and conditioned opiate withdrawal on memory consolidation*

Nana Baidoo[1], Michael Wolter[1], Francesco Leri[1], Boyer Winters[1]

[1]University of Guelph

Opiate withdrawal can be associated to a context through classical conditioning to produce conditioned withdrawal. To explore the role of conditioned withdrawal in memory processes, this research investigated whether conditioned withdrawal could impact memory consolidation. Two experiments in male Sprague-Dawley rats compared the effects of naltrexone-precipitated withdrawal and conditioned withdrawal on consolidation of object recognition memory. In Experiment 1, 3 mg/kg naltrexone (NTX) was administered immediately, or 6 hours, post-sample to morphine-naïve (MOR N) and morphine-maintained (MOR M) animals (osmotic mini-pumps; 10 mg/kg/day). In Experiment 2, (MOR N) and (MOR M) were confined for 2 hours in a distinctive chamber (CS+) following NTX injections (1 or 3 mg/kg) and in another chamber (CS-) following vehicle injections alternatively for 10 days. The effects of immediate or delayed (6 hrs) post-sample exposure to the CS+ and CS- were tested 7 days following removal of pumps. Experiment 1 found that post-sample 3 mg/kg NTX enhanced object recognition memory when administered immediately, but not 6 hours only in (MOR M) rats. Experiment 2 found that exposure to CS+ immediately, but not 6 hours, post-training enhanced object recognition memory and produced conditioned responses only in (MOR M) rats. These experiments indicate that both acute precipitated and conditioned withdrawal have significant and persistent facilitatory effects on memory consolidation and can play role in maintaining addictive behaviours.

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3-F-153 *The fate of an engram supporting a conditioned fear memory*

Sungmo Park[1], Paul W. Frankland[1], Sheena A. Josselyn[1]

[1]The Hospital for Sick Children

During an event representing a memory, neurons that are more excitable or active are recruited or allocated to an engram. Although we previously reported the process of allocation to an engram, it is unclear about the fate of the original engram and how it may change over time or with additional experience. Here we examined an engram supporting an auditory cued fear memory (in which a tone is paired with a footshock) in the lateral nucleus of the amygdala (LA). To manipulate the excitability of neurons, we used optogenetics allowing us to either activate (ChR2) or inhibit (NpHR3) the same neurons at different points in our experiment. First, we showed that optogenetically activating the original engram induces artificial memory recall either 1 d or 28 d post training. This finding suggests that although the original trace may be modified with time, a core ensemble is sufficient for memory recall. Second, we showed that even after behavioural extinction (presenting the 16 tones alone), optogenetically activating the engram induces memory recall. This finding is consistent with previous results showing that behavioral extinction requires "new learning" rather than a modification of the original memory trace. Finally, we showed that optogenetic extinction (that is, replacing the tone in the extinction training with optogenetic stimulation) essentially "erases" the memory trace, as the memory was no longer able to be retrieved by subsequent optogenetic stimulation, spontaneous recovery or reinstatement. Thus, these findings help us understand the fate of an engram once formed.

3-F-154 *Characterizing the role of the marmoset posterior parietal cortex in saccade generation*

Maryam Ghahremani[1], Kevin Johnston[2], Lauren Schaeffer[2], Stefan Everling[2]

[1]Robarts Research Institute, University of Western Ontario, [2]University of Western Ontario

Common marmosets are New World non-human primates that have recently gained prominence as useful animal models for neuroscientific research. Their lissencephalic cortex provides great advantage for the application of high-density electrophysiological techniques, to uncover the function of region-specific population of neurons contributing to prominent brain circuitries such as the oculomotor system. Fundamental oculomotor cortical areas such as the frontal eye fields and lateral intraparietal area (LIP) that are buried deep within sulci in macaques, are readily accessible at the surface of the brain in marmosets, making them ideal for high-density electrophysiological techniques. Resting-state fMRI studies have identified homologous frontoparietal oculomotor areas between macaques and marmosets, but knowledge of the

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functional properties of these putative areas in marmosets is still incomplete. Here we addressed this gap by probing the function of posterior parietal cortex (PPC) using intracortical microstimulation in two marmosets, implanted with 32-channel Utah electrode arrays. We observed that microstimulation of the left area LIP in both marmosets elicited saccadic eye movements at multiple sites, that exhibited a prominent contralateral upward bias, aligning with the previous literature on LIP stimulation in macaques. Saccade thresholds ranged from 50 to 240 μA and their onset latencies declined as a function of the amplitude of stimulation current. Our findings suggest that the marmoset PPC is homologous with that of the macaque, evident from its oculomotor function.

3-F-155 *Identification of functional role of medial prefrontal cortical neurons co-expressing D1 and D2 receptors*

Clémentine Quintana[1], Jean-Martin Beaulieu[1]

[1]University of Toronto

Dopamine neurotransmission plays a critical role in motor function, motivation, reward-learning, cognitive processes and neuropsychiatric pathologies. In medial prefrontal cortex (mPFC), both D1-class and D2-class receptors are found on pyramidal and non-pyramidal neurons. Dopamine may exert both direct and indirect effect on the excitability of mPFC pyramidal neurons inducing different behavioural responses. However, a recent study reported the existence in mPFC of small population (around 20%) of co-expressing DRD1 and DRD2 neurons (DRD1-DRD2 neurons)(X. Wei et al. 2018). We used combinations of transgenic reporter systems and quantitative translatome analysis to examine population of DRD1-DRD2 neurons in mPFC and observed a much higher proportion of these neurons up to 20% in layer II and approximatively 60% in layer V. According to the important involvement of mPFC dopamine neurotransmission in the context of cognitive function regulation, we used somatic CRISPR/Cas9 mediated knockout to investigate the functional role of mPFC DRD1-DRD2 expressing neurons in the regulation of behaviors. This comprehensive analysis of mPFC neurons provides indications for its functional implications in healthy and disease conditions. Heterogeneity of dopamine receptor expression in mPFC has to be taken into consideration during pharmacological intervention and assessment of functional and behavioral data.

3-F-157 *Effects of a maternal high-fat diet during pregnancy on working memory and it´s relation with serum glutathione levels in the Wistar rat pups*

Nadia Cortés-Alvarez[1], César Vuelvas-Olmos[1], Maria Pinto-González[1], Ricardo Pedraza-Medina[1], Jorge Guzmán-Muñiz[1], Jorge Collás-Aguilar[1], Norma Moy-Lopéz[1], Luz Baltazar-Rodriguez[1]

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[1]University of Colima

Maternal high-fat diet (HFD) consumption influences the neonatal health, including the neurodevelopment and cognitive abilities. However, the causal mechanism underlying is not fully elucidated. The aim was to analyze the effects of a HFD during gestation on working memory and it´s relation with serum glutathione (GSH) levels in the Wistar rat pups. We used pups from dams who were fed a balanced diet (BD, 6.2% fat energy) or HFD (42% fat energy) during pregnancy. We used the Eight-Arm Radial Water Maze to assess working memory (correct/incorrect working memory and reference memory errors). Evaluations were released at postnatal day (PND)28 to 42 and PND76 to 90. Subsequently, the ELISA technique was performed to identify the serum GSH levels. Results showed similar weights in both groups at PND42 ($p>0.05$); but at PND90, HFD pups were significantly heavier ($p=0.001$). About the working memory assessment, both at PND42 and 90, there was significant difference in all parameters evaluated ($p<0.05$). Also, HFD pups showed significantly lower serum GSH levels both at PND42 ($p=0.001$) and 90 ($p=0.002$). A correlation was found between the GSH serum levels and the correct working memory errors ($r=0.81$, $p<0.05$). Therefore, a maternal HFD during pregnancy could cause alterations on the GSH levels (suggesting an increase in oxidative stress) and working memory deficits both in early and adult stages in offspring. This work was supported by CONACyT (280424 and PN-2016-01-465) and PROFOCIE UCOL-CS 2014-2017. None of the authors have any conflict of interest to declare.

3-F-158 *Effects of contact sports practice on a computerized cognitive assessment in collegiate contact sport athletes*

César Vuelvas-Olmos[1], Nadia Cortés-Alvarez[1], Pedro Flores-Moreno[1], Jorge Guzmán-Muñiz[1], Norma Moy-Lopéz[1], Fabián Rojas-Larios[1]

[1]University of Colima

Contact sport are the most practiced sports, however, the direct or indirect contact of the head are implicated. Head impacts can cause changes in the brain, even when there are no outward signs of a concussion. The aim was to determine whether contact sport practice affects cognitive performance in collegiate sport athletes. Participants were 20 collegiate soccer players and 20 noncontacts collegiate sport athletes, who practiced along 6 months uninterrupted and without record of TBI. All athletes were assessed using the CogState Battery, which consists of six cognitive tasks that measure control motor visual, associated peer learning, psychomotor function, attention, working memory and executive function. There no found significant differences between contact sport group compared to noncontact sport group, according to the sex (females: 9% vs 22%, males: 91% vs 78%), age (22±1.4 vs 21±1.5) and years of education (14±1.1 vs 14±1.3). The contact sport athletes performed more poorly at two cognitive domains than noncontact sport athletes: Associated peer learning (contact group: accuracy (ACC) 1.39±0.22

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vs noncontact group: ACC 1.78±0.18; p=0.001) and working memory (contact group: Movements per second (MPS) 1.47±0.3, correct moves (CMV): 45±6 vs noncontact group: MPS 1.60±0.24, CMV: 51±4; p=0.003). There not found significant differences in the others cognitive domains. Therefore, repetitive head impacts may negatively impact the associated peer learning and working memory function in soccer players; even when there are no outward signs of an injury.

3-F-159 *Dissociable mitogen activated protein kinase pathways in the ventral hippocampus underlie delta-9-tetrahydrocannabinol-induced dysregulation of prefrontal cortical neural activity and cognitive deficits*

Roger Hudson[1], Tony Jung[2], Tya Vine[1], Walter Rushlow[1], Steven Laviolette[1]

[1]University of Western Ontario, [2]Western University

Mnemonic and attentional deficits are common neurocognitive impairments associated with cannabis use, and constitute core features of schizophrenia and other psychiatric disorders. However, the contributions of precise neurocircuitry and neurobiological mechanisms to these pro-psychotic impairments remain unknown. Given that direct projections between the ventral tegmental area (VTA) and medial prefrontal cortex (mPFC) facilitate attention and working memory processing in the ventral hippocampus (VHipp), we explored the hypothesis that intra-VHipp delta-9-tetrahydrocannabinol (THC) dysregulates mPFC-VTA neural activity to elicit cognitive deficits via modulation of local molecular signaling cascades. THC elicited c-Jun N-terminal kinase (JNK)-dependent deficits in short-term and working memory, social cognition, and attentional output, without affecting sensorimotor gating. mPFC pyramidal phasic bursting activity, and the number of spikes per each burst were reduced by intra-VHipp THC. Power spectral density analyses demonstrated increased mPFC beta, gamma, and epsilon LFP band power following THC. Cross correlation analysis revealed diminished mPFC-VTA synchronization within theta and gamma bands following THC via an extracellular signal-regulated kinase (ERK)-dependent mechanism, suggesting aberrant functional connectivity between the two regions. Thus, THC reduces mPFC-VTA information flow via dissociable JNK-ERK signaling cascades to elicit cognitive deficits and attentional impairments, suggesting implications for cannabis phytochemicals in neuropsychiatric disorders.

3-F-160 *Imaging neuronal allocation to an episodic-like memory in the rodent hippocampus*

Andrew Mocle[1], Adam Ramsaran[1], Blake Richards[1], Paul Frankland[1], Sheena Josselyn[1]

[1]University of Toronto

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Episodic-like memories are thought to be encoded by the activity of a sparse ensemble of neurons in the hippocampus of rodents, termed its memory engram. Recent work characterizing engrams of different types of memories have pointed to a common excitability-dependent mechanism of neuronal allocation to an engram. Neurons that are highly-excitable relative to their neighbours will be preferentially recruited to encode a memory. This enhanced excitability is typically produced by manipulating a sparse population of neurons either by genetic or optogenetic methods. Furthermore, it is thought that recall of a previously acquired memory transiently enhances the excitability of its engram, thereby allowing its modification, updating, or linking with new memories. Despite strong evidence for an excitability-dependent mechanism for neuronal allocation, it primarily comes from studies involving the experimental manipulation of neuronal excitability. It is possible that these manipulations push neuronal excitability beyond of the normal biological range, and may therefore not recapitulate endogenous mechanisms. In this study, we take advantage of a custom miniaturized microscope to investigate endogenous mechanisms of neuronal allocation. Our data suggests that highly excitable principal neurons in CA1 are more likely to be allocated to a hippocampal memory trace. Furthermore, we show that the excitability-dependent competition likely occurs between small ensembles of neurons that are present immediately before training, and which are reactivated to support recall.

3-F-161 *Morphometric and spine density analysis of pyramidal neurons in a mouse model of sporadic Alzheimer's disease*

Rasha Mehder[1], Brian Bennett[1], R. David Andrew[1]

[1]Queen's University

The study of late-onset Alzheimer`s disease (LOAD) has been hindered by the lack of animal models. We have developed an oxidative stress-based model of LOAD based on gene deletion of aldehyde dehydrogenase 2 (Aldh2). These knockout (KO) mice exhibit a progressive decline in recognition and spatial memory, and in other AD-like pathologies. To determine if altered neuronal structure can account for the observed memory deficits, dendritic morphology of one year old KO and WT mice was compared using branched structured analysis and Sholl analysis of dorsal (dCA1) and ventral (vCA1) hippocampal pyramidal neurons (PNs), and the overlying PNs of layer V 1º visual neocortex (V1). Morphology and complexity of dCA1 (but NOT vCA1) PNs from KO mice showed significant reductions in apical and basal dendritic length, and significantly fewer dendrite intersections, ends, and nodes. The spine density along dCA1 apical and basal dendrites was similar to WT controls. V1 dendritic complexity was slightly but significantly reduced in KO vs WT. These data indicate that dCA1 dendritic complexity is significantly reduced in KO mice whereas vCA1 dendrites appear unaltered. We found no change in the size of pyramidal cell bodies or their number of extending dendrites. Thus dCA1 neuronal arbors are pruned back, but the remaining dendrites display a near-normal density of spines. It is likely that this is the specific

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structural basis for the cognitive deficits seen in our LOAD model, given the central role of the dorsal hippocampus in both recognition and spatial memory.

3-F-162 *Effects of levodopa on craving for alcohol in abstinent alcoholics*

Kathryne (Kasey) Van Hedger[1], Nole Hiebert[1], Ivan Witt[1], Ken Seergobin[1], Penny MacDonald[1]

[1]University of Western Ontario

Craving is a common experience in individuals with substance use disorders. It refers to the urge or desire to use a drug and can vary in intensity. One neurobiological explanation for the development of craving is through a process of incentive salience, where addictive drugs co-opt the endogenous dopamine system and sensitize it to reinforce future drug use. As a result of this, individuals with substance use disorders are known to have disrupted dopaminergic signaling, with previous research showing increased ventral striatum responses to drug cues. In this study, we sought to evaluate the effects of levodopa, a dopamine precursor, on behavioral ratings of alcohol craving in a sample of abstinent self-identified alcoholics recruited from local area Alcoholics Anonymous meetings. Participants were pre-screened for mental and physical health issues prior to completing two sessions involving cue-reactivity tasks where they rated their feelings of craving for alcohol while viewing alcohol-related pictures. Before each task participants were pre-treated with either levodopa or placebo. Among participants who reported any craving for alcohol, significantly less craving was experienced following levodopa compared to their placebo session ($p < .05$). These findings are consistent with previous levodopa studies indicating that it decreases activation in the ventral striatum. Follow-up functional magnetic resonance imaging measures of striatal and cortical activation in response to alcohol cues will help clarify the mechanism of this decrease in craving.

3-F-163 *Determining parameters for safer therapeutic deep brain stimulation that preserves healthy medial temporal lobe network function and memory*

Mary McIntosh[1], Ron Levy[1]

[1]Queen's University

Neurological disorders have become the leading cause of disability and Epilepsy is among the top 4 most prevalent. Many individuals with epilepsy have debilitating seizures that can't be treated and resort to Deep brain Stimulation (DBS) as an experimental therapy. Currently, Medial Temporal Lobe (MTL) DBS is programmed by monitoring behavior and disease symptoms without an understanding of how it affects memory networks. MTL DBS has shown limited efficacy for treating seizures perhaps due to interruption of normal electrical interactions. Some studies show

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that it impairs memory and others show that it improves memory so underlying physiological mechanisms require further study. Our hypothesis is that there is a safe therapeutic window of parameter space for MTL stimulation where we can preserve networks for memory and cognitive function. Effects of DBS were studied in a healthy non-human primate (NHP) model so that they were not confounded by manifestations of pathology. Our neurosurgical and electrophysiological techniques allowed us to characterize neuronal, laminar and MTL network interactions in NHP memory circuits as they navigate a spatial memory task in Virtual Reality. Our results show that therapeutic stimulation disrupts state-dependent network connectivity and field evoked potentials before memory impairments or cognitive deficits manifest. Understanding how DBS affects MTL memory networks can improve the safety and efficacy of human neuromodulation. The effects of MTL DBS in healthy individuals will inform how it is used as a clinical therapy.

3-F-164 *Structural brain differences between cognitively impaired patients with and without apathy*

Nathan Chan[1], Philip Gerretsen[2], Daniel Blumberger[2], Fernando Caravaggio[2], Eric Brown[1], Ariel Graff-Guerrero[2]

[1]University of Toronto, [2]Centre for Addiction and Mental Health

Objectives: Apathy is associated with cognitive deficits and worse outcomes in patients with cognitive impairment. Disruptions of frontostriatal circuits and frontotemporal association areas are associated with apathy. We examined structural brain differences between patients with and without apathy who exhibit similar levels of cognitive impairment. Methods: Apathy was assessed in cognitively impaired patients from the Alzheimer's Disease Neuroimaging Initiative with the Neuropsychiatric Inventory. Patients with apathy were matched to those without apathy by age, sex, apolipoprotein 4 allele number, Mini-Mental State Exam score, and mild cognitive impairment or AD diagnosis in matched strata by coarsened exact matching. Cortical thickness and subcortical volume differences from structural MRI were tested with a total intracranial volume-controlled and false discovery rate-corrected (q=0.10) mixed-effects MANCOVA. Results: Relative to patients without apathy (n=165), the bilateral medial orbitofrontal cortex and left rostral anterior cingulate were smaller in patients with apathy (n=71), whereas the left superior temporal cortex, left banks of the superior temporal sulcus, and right putamen were larger. Conclusions: Patients with apathy exhibit larger left lateral temporal areas and smaller bilateral medial frontal areas compared to patients without apathy. Our results confirm that frontostriatal circuit disruptions are associated with apathy in cognitively impaired patients and suggest that distinct neuropathologies may underlie similar levels of cognitive impairment.

3-F-165 *Goal states modulate the outcome of cortical stimulation*

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Becket Ebitz[1], Tirin Moore[2], Benjamin Hayden[1]

[1]University of Minnesota, [2]Stanford University and Howard Hughes Medical Institute

In variable or uncertain environments, solely "exploiting" rewarding options is not the best strategy. Instead, intelligent decision-makers also "explore" alternatives: they will forgo some immediate rewards in order to learn or discover new opportunities. Fifty years of neurobiological research has uncovered much about the neural basis of exploitative decision-making. How do these mechanisms change when the goal is exploration, rather than maximizing immediate reward? One possibility is that we explore by releasing prefrontal control over behavior, perhaps through disrupting the patterns of prefrontal activity that implement exploitative goals. Here, we tested this hypothesis in the primate frontal eye fields (FEF), a prefrontal region important for controlling decision-making and attention. We formalized our hypothesis in an attractor network model of the FEF, which explained salient features of the neural activity and made a novel prediction: if the dynamics that implement control in the FEF are disrupted during exploration, it should be easier to perturb the FEF during exploration. We tested this hypothesis by lowering stimulating electrodes into the FEF and measuring how the effects of stimulation changed across goal states. Consistent with the predictions of the model, we found that stimulation was both more effective and more accurate when it was delivered during exploration. Together, these results support the hypothesis that we explore, in part, via releasing prefrontal control over behavior--a simple, efficient, and sufficient approach to the problem of exploration

3-F-166 *L-dopa alters brain activity associated with regularity detection*

Abdullah Al Jaja[1], Nole Hiebert[2], Bjorn Herrmann[1], Ken Seergobin[2], Jessica Grahn[1], Penny MacDonald[2]

[1]Brain and Mind Institute/ Western University, [2]University of Western Ontario

The brain is particularly tuned to the presence of regularities (e.g., repetitions) within auditory scenes, potentially as means of facilitating the segregation of different superimposed auditory streams. Processing regularities is thought to involve the interplay of several brain areas such as the auditory cortex, inferior frontal gyrus (IFG), and possibly the hippocampus. We observed recently that neural signals that indicate regularity processing (RP) are reduced in older people. In addition, 3,4-dihydroxyphenethylamine (L-dopa) reduced the same neural signals in healthy older adults and patients with Parkinson's disease. The aim of the current study was to investigate how and where in the brain L-dopa affects neural signatures of RP. We hypothesized that L-dopa overdoses dopamine-replete brain regions that mediate RP. Functional magnetic resonance imaging was recorded from eighteen healthy undergraduates, once on L-dopa/carbidopa 100/25mg and once after taking a placebo. Participants listened to two different auditory stimuli that consisted of short tone pips that either contained a regularity (i.e., a repeating pattern) or did

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not contain a regularity. Off medication, significant activation arose in the IFG and primary auditory cortex when the regular condition was contrasted with either random or silent condition and this effect disappeared on medication. This presentation examine the global effects of L-dopa on neural signatures of RP. Our results increase our understanding of RP and favors the role of the ventral tegmental area in facilitating this process.

3-F-167 *Neural bases of note normalization in absolute pitch*

Stephen Van Hedger[1], Shannon Heald[2], Howard Nusbaum[2]

[1]Western University, [2]University of Chicago

Objective: Individuals with absolute pitch (AP) - the ability to identify any musical note without the aid of an external reference note - can recognize notes across timbres and octaves as belonging to the same abstract category (e.g., C). The neural mechanisms that underlie this normalization process are unclear. Here, we use functional magnetic resonance imaging (fMRI) to investigate the networks that support note categorization in acoustically variable environments. Method: On each trial, AP participants listened to a rapid sequence of notes and pressed a button whenever they heard a specified target note (e.g., C). The note sequences were selected from a single instrument (piano or violin), from a single octave (low or high), or randomly selected notes from the two instruments or octaves with trials blocked by timbre or octave variability. Results: Participants were slower to recognize notes in mixed-instrument and mixed-octave trials. Imaging results showed greater activation of the right angular gyrus (AG), with enhanced functional connectivity (FC) between primary auditory cortex and right AG for mixed-instrument trials. Mixed-octave trials resulted in greater fronto-parietal activation, with enhanced FC between primary auditory cortex and left inferior frontal gyrus. Conclusion: These findings provide evidence for an active mechanism in note normalization in AP. Uncertainty regarding the timbre and octave of musical notes require additional processes of perceptual accommodation and attention reorientation before a note can be recognized and categorized.

3-F-168 *Cannabinoid receptor expression in a model of addiction vulnerability*

Ali Gheidi[1], Lora Cope[1], Christopher Fitzpatrick[1], Claire Barcelo[1], Jonathan Morrow[1]

[1]University of Michigan

Cannabinoids are known to regulate dopaminergic activity, and increased dopaminergic responses to conditioned cues are the most consistently reported neurobiological correlates with increase attribution of motivational salience. Aberrant motivational salience attribution has been

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proposed as a pathological mechanism of addiction. One behavioral model used to measure motivational salience attribution involves repeatedly pairing a neutral conditioned cue (e.g. a retractable lever) with the response-independent delivery of a reinforcer (e.g. a food pellet). Under these conditions, animals will learn to either "sign-track", i.e. approach and contact the lever-cue, or "goal-track", i.e. approach the food cup. In contrast to goal-tracking, sign-tracking is dopamine-dependent, indicates an attribution of motivational salience to the cue, and is correlated with vulnerability to both addiction-like behaviors in rats. We hypothesized that individual differences in the cannabinoid system might correlate with sign- and goal-tracking behavior. To test this hypothesis, we performed radiolabeled in situ hybridization for CB1 receptors and fatty-acid amide hydrolase (FAAH) in sign- and goal-tracking rats. No differences were observed in FAAH levels in the dorsal/ventral hippocampus or the prefrontal cortex. However, CB1 levels in the prelimbic cortex were higher in sign-trackers than in goal-trackers. Future studies will determine whether manipulation of cannabinoid signaling in this region can selectively influence sign- and goal-tracking behavior.

3-F-169 *Ultra-rapid formation of event associations in single neurons in the medial prefrontal cortex*

Kaori Takehara-Nishiuchi[1], Maryna Pilkiw[1], Mark Morrissey[1]

[1]University of Toronto

Seminal human imaging studies show that the magnitude of the activation of prefrontal cortex and hippocampus is predictive of whether experiences are later remembered. Parallel animal studies show that medial prefrontal cortex (mPFC) undergoes functional remodeling at the time of encoding and that the integrity of mPFC is necessary for encoding-induced gene expression in hippocampus. To investigate neural ensemble dynamics underlying mPFC's role in memory encoding, we analyzed firing patterns of 30+ single neurons simultaneously recorded while naïve rats received a sequence of auditory stimuli and aversive eyelid shock for the first time. For 10-15 minutes, the auditory stimulus was presented every ~30 seconds. Subsequently, the shock was delivered after each presentation of the stimulus with a fixed interval. Principal component analysis revealed the main source of firing rate variance was an abrupt transition that occurred immediately after the first presentation of the shock. The population-level change was driven by ~15% of neurons that increased their baseline firing rates immediately after the first shock presentation. Initially, these neurons responded only to the shock; however, within a few stimulus-shock parings, they rapidly developed reliable responses to the stimulus. Thus, contrary to the traditional view that hippocampus learns first, and neocortex follows, a dedicated class of mPFC neurons associate neutral and innately salient events on the fly, which may serve as a relevancy signal that facilitates encoding of those events in hippocampus.

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3-F-170 *An isolated brief seizure produces robust deficits in trace fear learning*

Teresa Ann-Maletta[1], Emily Horsey[1], Lianne Brandt[1], Neil Fournier[1]

[1]Trent University

Seizure-associated memory deficits are generally thought to only arise during chronic epilepsy. However, there is evidence that even a single brief generalized seizure can result not only short- but also long-term memory deficits. In the present study, we set out to examine whether a single brief generalized seizure induced by the chemoconvulsant pentylenetetrazole (PTZ) can disrupt normal trace fear learning in Long-Evans rat--a rat strain that is particularly resistant to the effects of PTZ. Rats were treated with PTZ or saline either 2 hr or 24 hrs before undergoing a standard trace fear learning task. Short-term memory (STM) and long-term memory retention tests were carried out 3 hrs and 24 hrs after training. While non-kindled and PTZ-treated rats showed similar post-shock acquisition freezing levels and responsiveness to the foot shock during conditioning, rats that were administered PTZ 2 hrs before training displayed significantly lower levels of freezing during the STM and LTM retention tests. In contrast, there was no difference in freezing between during STM or LTM tests for rats that were treated PTZ or saline 24 hrs before conditioning. We are currently examining the role of mTORC signalling as a potential molecular mechanism contributing to impairments in memory after a single generalized seizure.

3-F-171 *Automated touchscreen tasks reveal early cognitive dysfunction caused by mutant TDP-43 in an FTD/ALS mouse model*

Keon Coleman[1], Roseane Franco[1], Matthew Cowan[1], Julliane Joviano-Santos[1], Jane Rylett[1], Vania Prado[1], Lisa Saksida[1], Marco Prado[1], Timothy Bussey[1], Flavio Beraldo[1]

[1]University of Western Ontario

TAR-DNA-binding protein 43 (TD-P43) misfolding and aggregation is a major pathological hallmark of Fronto-Temporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS) but, has also impact in Alzheimer's and Parkinson's. FTD and ALS are characterized by motor and cognitive impairments. However, robust cognitive phenotypes related to TDP-43 proteinopathy have not yet been explored in mouse models of FTD/ALS. In this study, we used the Bussey-Saksida touchscreen technology for assessing executive function in the transgenic FTD/ALS mouse model TDP-43Q331K_low. It has been reported that these mice show motor impairments at 12 months of age. However, cognitive dysfunction has not yet been evaluated in this mouse line. Attention and learning/cognitive flexibility (major constructs affected in FTD/ALS) were assessed in TDP-43Q331K_low male mice using the Five Choice Serial Reaction Time Task (5-CRSTT) and Pairwise Visual Discrimination (PVD) task. In 5-CRSTT, TDP-43Q331K_low mice (5-6-month-old) present greater number of omissions and compulsive-like behaviour. Interestingly, in PVD task TDP-43Q331K_low mice were impaired in the acquisition and reversal phase of the

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task, suggesting that these mice present learning and potentially cognitive flexibility deficits. These results indicate that the TDP43Q331K-low mice present attentional, learning and cognitive flexibility deficits, similar to the cognitive impairments observed in humans affected by these diseases, and the usefulness of the touchscreen tasks for the development of new therapeutic approaches for ALS/FTD.

3-F-172 *Neuroprotective role of L-theanine on a schizophrenia-like phenotype induced by chronic adolescent THC exposure*

Marta De Felice[1], Justine Renard[1], Hanna Szkudlarek[1], Roger Hudson[1], Brian Pereira[1], Susanne Schmid[1], Walter Rushlow[1], Steven Laviolette[1]

[1]University of Western Ontario

L-theanine, a glutamate derivative extracted from green tea, modulates brain dopamine, GABA and serotonin levels. Clinical evidence shows that L-theanine is able to promote relaxation, mood enhancement, concentration and neuroprotection in schizophrenic patients. We showed that chronic administration during adolescence of delta-9-tetrahydrocanabinol (THC) in rats, induced schizophrenia-like behavioural deficits associated with a state of hyper-dopaminergia in the ventral tegmental area (VTA), an excitatory/inhibitory imbalance in the prefrontal cortex (PFC) and disruptions in cortical gamma oscillations during the desynchronized states. Hence, we hypothesized that L-theanine might provide beneficial effects against adolescence THC-induced schizophrenia-like aberrations. Adolescent rats were treated from postnatal day (PND) 35 to 45 with L-theanine (10mg/kg i.p.) or saline, 10 minutes prior i.p. injections of increasing doses of THC (2.5mg/kg - 10mg/kg, twice a day) or vehicle. At adulthood (PND 75), behavioral tasks and in vivo single unit electrophysiological recordings of PFC pyramidal and VTA dopaminergic cells were performed. Our results show that adolescent pre-administration of L-theanine prevented the long-term psychotomimetic symptoms induced by chronic THC exposure and it was able to normalize the profound neuronal alterations in the adult mesocorticolimbic circuit, including gamma oscillatory activity. Overall, our findings suggest that L-theanine might represent a prominent therapeutic strategy for treatment of neuropsychiatric conditions, such as schizophrenia.

3-F-173 *Psychopathic traits modulate functional connectivity metrics of drug- and food-reactivity in both dependent and non-dependent participants*

William Denomme[1], Matthew Shane[1]

[1]University of Ontario Institute of Technology

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Research has demonstrated that stable psychopathic traits modulate dynamic neural reactivity to drug and non-drug rewards. However, experts have begun to assess the dynamic spatiotemporal connectivity between regions underlying drug reactivity. To this end, we assessed how psychopathic traits modulated functional connectivity (FNC) throughout our previously published cue-reactivity task (Denomme et al., 2018) among 101 probation parolees viewing drug- and food-related videos while placed in an fMRI. We observed that total PCL-R (Hare, 2003) scores were associated with increased FNC between our orbitofrontal cortex ROI seed and several clusters throughout the brain when exposed to all videos, with cluster peak-voxels located within the postcentral gyrus, supramarginal gyrus, and the insula. In response to drug videos specifically, PCL-R scores were associated with increased FNC between the dorsomedial prefrontal cortex ROI seed and peak-voxels within the postcentral gyrus, as well as FNC between the orbitofrontal cortex ROI and peak-voxels within the supramarginal, postcentral, and angular gyrus, precuneus, and insula. There were no significant correlations between PCL-R scores and FNC while observing food-related videos. These results further our understanding of the functional neural underpinnings of reward processing in psychopathy, how it may be modulated by the type of reward, and further elaborate neuroscience targets for research and treatment of psychopathy.

3-F-174 *Transient cholinergic signal during aversive events modulate prefrontal network state during memory encoding*

Gaqi Tu[1], Samuel Gillman[1], Xiao Yu[1], Kaori Takehara-Nishiuchi[1]

[1]University of Toronto

The basal forebrain (BF) cholinergic system provides cholinergic inputs to the entire cortex and was thought to slowly modulate cortical activity. In contrast, recent studies found that cholinergic activity fluctuates at millisecond precision in response to stimuli with innate and learned salience. These findings, along with the established link between acetylcholine and learning, led us to hypothesize that the transient, event-locked cholinergic signal improves cortical neural responses to those events and in turn facilitates encoding of event memories. Among various targets of BF cholinergic innervation, the medial prefrontal cortex (mPFC) plays a key role in event memory. We thus optogenetically inhibited cholinergic terminals in mPFC during neutral or aversive events while mice associated those events over a temporal gap. When inhibiting cholinergic activity during the neutral event, there was a trend for impairment in association formation. In contrast, the same manipulation during the aversive event facilitated the learning. The enhanced learning was accompanied by increased expression of neuronal activity marker, c-Fos in somatostatin-positive interneurons and excitatory neurons in the mPFC. Together, these findings did not support a view that transient cholinergic activity during aversive events serves as a reinforcement signal. Rather, it modulates mPFC network state during memory encoding by differentially recruiting local excitatory and inhibitory neurons.

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3-F-175 *Systems consolidation impairs behavioural flexibility*

Sankirthana Sathiyakumar[1], Blake Richards[1]

[1]University of Toronto

Prior learning in an environment can either promote or inhibit behavioural flexibility. Previous research suggests that systems consolidation, a long-term process that alters memory traces, may alter the degree to which prior learning interferes with flexibility. However, exactly how systems consolidation affects behavioural flexibility is unknown. Here, we tested how systems consolidation affects: (1) adaptations to reductions in the value of specific actions and (2) adaptations to changes in the optimal sequence of actions. Mice were trained to obtain food rewards in a Y-maze by alternating nose pokes between three arms. During initial training, all arms were rewarded and no specific sequence was required to maximize rewards. Then, after either a 1 day or 28 day delay, we changed the task. In one group, we devalued pokes in one arm, and in another group, we reinforced a specific sequence of pokes. We found that after a 1 day delay mice adapted easily to the changes. In contrast, mice given a 28 day delay struggled to adapt, especially in the case of changes to the optimal sequence of actions. These data demonstrate that systems consolidation impairs behavioural flexibility, particularly for changes to the sequence of actions that must be taken.

3-F-176 *Genetically-predicted DRD4 gene expression in frontal cortex is associated with sex and SES differential expression of impulsivity and sugar intake*

Afroditi Papantoni[1], Andre Portella[2], Robert Levitan[3], Patricia Silveira[2], Susan Carnell[1], Laurette Dube[2]

[1]Johns Hopkins University, [2]McGill University, [3]University of Toronto

Adolescence is a period characterized by maturational processes that occur in brain regions responsible for cognitive control and reward-seeking that may underpin excessive consumption of palatable high fat and high sugar "junk" foods. Dopamine receptor 4 (DRD4) activity in frontal brain areas is implicated in modulating behavioral responses to the environment in several domains, including eating behavior, decision making and incidence of chronic diseases. In a sample of 78 adolescents (40 boys and 38 girls from Baltimore, Maryland/US, aged 14-18y), we analyzed main effects and the interaction between SES (low income cutoff) and genotype-predicted DRD4 gene expression level in the frontal cortex (PrediXcan), in the domains of eating behavior (Multi-item ad lib meal test) and approach/avoidance motivational scale (BIS/BAS). Linear regression models stratified by sex and adjusted for BMI z-score, and race showed no significant associations in boys. However, in girls, impulsivity was negatively correlated to SES

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(p=0.037), and DRD4 correlated negatively with sugar intake in the low-income group and positively in the high-income group (p=0.039 for interaction, controlling for BMI z-score and race). The genetically-predicted gene expression of prefrontal DRD4 interacts with sex and the environmental context, affecting eating behavior but not inhibitory control. This can have implications for the mechanistic investigation of differential susceptibility, precision medicine and public health interventions.

3-F-177 *Motivation and executive functions, craving, and snacking behavior: an experience-sampling comparison between restrained and unrestrained eaters*

Ji Lu[1], Laurette Dube[2]

[1]Dalhousie University, [2]McGill University

Unhealthy eating is triggered by food cues with high reinforcement value, while many people adopt restrained eating for weight control. This study aims to assess the interactions between neurocognitive functions and environment by linking snacking behavior with individual differences in motivational reactivity to rewarding cues and executive functions related to self-control. 109 adult women performed a computer neurobehavioral test (Affective Shifting Task) to assess motivational reactivity, inhibition control, and cognitive flexibility. Parameters are estimated for attentional bias to rewarding cues, task performance of stopping responses to rewarding cues, and adaptability to new task rules. The participants also reported a 10-day sampling study reporting their physiological status, high reinforcement food(HRF) cravings and snacking behaviors six times a day. Craving was a strong predictor of HRF snacking, while this predictive power of craving was a function of one's neurocognitive traits. For restrained eaters, attentional bias to rewarding cue was positively associated with craving, while across un-restrained eaters, better cognitive flexibility was associated with less likelihood of following a craving, suggesting that their ability to shift attention away from rewarding cues helped them to attend to activities other than eating. In contrast, for restrained eaters, higher inhibitory control was associated with a stronger craving. Results are discussed in terms of their potential account for the poor real-world performance of restrained eaters in controlling eating.

3-F-178 *Characterizing neurogenesis-mediated forgetting in the water maze paradigm*

Chunan Duan[1], Lina Tran[2], Sheena Josselyn[1], Paul Frankland[1]

[1]University of Toronto, [2]The Hospital for Sick Children

Objective: Recently, neurogenesis (NG) in the dentate gyrus (DG) has been identified as a potential mechanism underlying forgetting. The current study aims to characterize the

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behavioural outcome of NG-induced forgetting in the water maze paradigm. Methods: Mice were trained in water maze for 4 days. We then used voluntary running to increase NG in the experimental group, while the control group remained sedentary. Both groups were tested for their memory after a 42-day delay. We acquired precise positional information of the mice and quantified forgetting through sub-second analyses of entropy and spatial bias. We then measured the level of NG by counting the number of cells expressing doublecortin, a marker for immature neurons, in the DG of all mice. Additionally, to establish the behavioral footprint of forgetting in the water maze paradigm, we compared NG-induced forgetting and other types of catastrophic forgetting, including those observed in infantile amnesia (IA) and Alzheimer's disease (AD). Results: The runners showed increased NG and worse memory. Fine-grained analyses of probe trial performance yielded a strong positive correlation between forgetting and the level of NG in all mice. Preliminary data on the forgetting behavior of IA and AD resembled that of NG-mediated forgetting, substantiating the interpretation that increasing NG results in forgetting. Conclusion: Taken together, our data demonstrate that hippocampal NG plays a crucial role in pruning memory precision in a quantitative manner.

3-F-179 *NEUROCHEMICAL and behavioural effects of stage-dependent ethanol exposure on novel tank response in juvenile zebrafish*

Celine Bailleul[1], Samuel Nguyen[1], Amanda Facciol[1], Robert Gerlai[2]

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

Zebrafish have become a popular model organism for the analysis of the behavioural and biological mechanisms underlying fetal alcohol spectrum disorders (FASD). Several studies have investigated the long-term behavioural and neurochemical effects of acute embryonic alcohol exposure in adult zebrafish, however, little is known about the effects of embryonic ethanol exposure in juvenile zebrafish. Furthermore, potential developmental-stage dependent effects of embryonic alcohol exposure have not been systematically analyzed. Here, we expose zebrafish embryos to ethanol at different developmental stages (6hpf, 10 hpf, 16 hpf, 24, hpf, 36 hpf, 48 hpf) and measure the resulting behavioural and neurochemical changes in one-month old AB zebrafish. We employ the novel tank task, an anxiety paradigm and use HPLC to quantify dopamine, serotonin and their metabolites from whole brain extract. Our results demonstrate significant developmental stage dependent effects of alcohol on certain behavioural responses. We are currently completing our HPLC analyses. We anticipate a correlation between behavioural and neurochemical effects of ethanol. We hope these findings will further our understanding of the behavioural and neural deficits commonly associated with FASD.

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3-F-180 *Virtually-simulated exchange of social touch between humans interacting as avatars hinders interpersonal affiliation*

Garima Saini[1], Marigrace Noronha[1], Anna Lomanowska[1]

[1]University of Toronto Mississauga

Online multiuser virtual environments are a popular medium for social interactions that resemble many aspects of face-to-face contact. Many of the physical components of real-life interactions can be simulated in these virtual contexts through visual and auditory cues, however tactile components of social contact are difficult to replicate virtually. Previous studies have explored digital simulation of social touch using haptic devices, but little is known about how the visual representation of social touch is perceived and integrated into a virtual interpersonal experience. The present research examined how the exchange of virtual social touch mediated by simulated 3-dimensional human characters, or avatars, within an online virtual environment influences interpersonal affiliation towards an interaction partner. Behavioural, self-report, and physiological measures (skin conductance, heart rate) were collected over two studies to examine the effects of virtual touch on the impressions formed of an interaction partner and on physiological arousal experienced during the virtual interaction. Results from both studies demonstrate that the exchange of virtual touch while interacting with an unfamiliar partner negatively affected the impressions formed of the partner but did not affect the level of physiological arousal during the interaction compared to a control no-touch condition. The findings suggest that, unlike the positive influence of social touch observed in typical face-to-face interactions, the virtual representation of social touch hinders social affiliation.

3-F-181 *Dissociable effects of tetrahydrocannabinol and cannabidiol on prefrontal cortex-dependent executive function and affective processing*

Hanna Szkudlarek[1], Sagar Desai[1], Justine Renard[1], Brian Pereira[1], Christopher Norris[2], Christina Jobson[1], Nagalingam Rajakumar[1], Brian Allman[1], Steven Laviolette[1]

[1]University of Western Ontario, [2]University of Kentucky

Medical and recreational use of cannabis is constantly increasing, despite considerable evidence correlating marijuana use with the development of schizophrenia-like symptoms. Out of >100 phytocannabinoids present in cannabis, tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most prevalent bioactive constituents that interact with multiple neurotransmitter pathways implicated in cognitive and affective functions directly in the prefrontal cortex (PFC). Previous research showed that TCH exposure may promote the development of psychosis, while CBD may be beneficial in the treatment of neuropsychiatric disorders and counteract THC effects. In the present study we show that acute intra-PFC infusions of THC in rats increase anxiety in the elevated plus maze test while producing no impairments of executive function. Co-infusion of CB1

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receptor antagonist (AM251) blocked anxiogenic THC effects implicating that increased PFC endocannabinoid tone might contribute to pathological anxiety states. On the contrary, acute intra-PFC infusion of CBD impaired attentional set-shifting and spatial working memory without interfering with affective behaviors such as anxiety or sociability. The effects of CBD were mediated via 5-HT1a receptor-dependent mechanisms. Nevertheless, CBD application produced ameliorative effects during states of cortical disruption induced by NMDA receptor blockade and prevented THC-induced anxiety. Our data suggest that the prefrontal effects of CBD may have divergent outcomes on cognitive flexibility and working memory as a consequence of existing pathology.

3-F-182 *Downstream target proteins of mTOR signaling are differentially modulated during motor skill learning*

Maxence Brouillette[1], Michel Cyr[1]

[1]UQTR - Université du Québec à Trois-Rivières

The capacity to learn new motor skills is fundamental for our daily activities and our ability to adapt to challenging environments throughout life. However, the spatiotemporal organization and functions of the critical molecular determinants responsible for motor skill learning are still under investigation. Our recent work has identified the mTOR kinase as an important molecular actor involved in long-lasting forms of synaptic and behavioral plasticity during motor learning in the striatum and hippocampus structures. The present study is exploring the role of mTOR's downstream proteins, P70S6K and 4E-BP2, in the learning processes associated with the accelerating rotarod test in mice. Rotarod performances were evaluated for 10 trials on day 1, 2, 3, 4 and 8. Mice showed rapid improvements within the first training day whereas at the second and third days, their scores improved slowly and reached a plateau. Post-translational modifications will be evaluated using Western blot and immunofluorescence technique. Preliminary results propose that 4E-BP2 is associated with motor learning rather than motor execution in both striatum and hippocampus structures, whereas P70S6K activity is not implicated. These experiments will establish the molecular mechanisms of the post-translational modifications of mTOR, 4E-BP2 and P70S6K proteins as well as their importance in the complex motor learning process.

3-F-183 *Saccadic time compression is influenced by visual stimulus novelty*

Amirhossein Ghaderi[1], George Tomou[1], John Douglas Crawford[1]

[1]York University

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Previous findings showed that saccades compress time (Morrone et al., Nature neuroscience 2005) while stimulus novelty expands it (Pariyadath & Eagleman, PLoS One 2012). These opposite distortions are not explained by current timing models based on a scalar framework. Here, we used an oddball/saccade paradigm to examine and model the interaction of these effects. Ten participants judged the duration of an oddball stimulus (between 140 and 260 ms) that was back-projected on a large screen. A standard stimulus (200 ms) was presented (1 to 3 times) before the oddball. There were three blocks (one saccade, two fixation controls with comparable retinal or spatial configurations). In the saccade block, participants were cued to perform a saccade 100 ms before oddball presentation and online eye tracking was performed. We compared individual timing performance. Repeated measure ANOVA revealed significant main effects of condition and number of repetitions. There was also a significant interaction, which suggests that, although the time compression occurred in the saccade condition, this effect was diminished by novelty of stimulus. Conversely, there was a time dilation of oddball in both saccade and fixation conditions. Overall, we conclude that the effect of stimulus novelty on perceived time is more dominant than the effect of a saccade. These results support non-scalar accumulative properties of visual timing that can be simulated by a linear vector timing model (Ghaderi et al., PloS one 2018). Grant Support: NSERC Discovery Grant, VISTA Fellowship, supported by the CFREF.

3-F-184 *Molecular markers of fear learning in brain and blood: focus on doublecortin (DCX)*

Marissa Maheu[1], Sumeet Sharma[2], Kerry Ressler[1]

[1]Harvard University, [2]Emory University

Background: Although considerable evidence implicates doublecortin (DCX) in neurogenesis and neural development, little is known about its function in non-neurogenic adult brain regions. The current study seeks first to explore whether fear learning is associated with altered amygdala (AMY) DCX expression and, second, to assess the utility of any such changes as predictive markers of fear learning. Methods: C57BL/6 mice underwent associative fear conditioning in which tones were paired with foot shock, followed by fear expression, extinction, and/or generalization testing. AMY tissue and blood collected after sacrifice was employed for immunoblotting (n=8), qRT-PCR (n=8), or RNA sequencing (n=4). Results: Fear learning was found to modulate AMY DCX protein levels; by 24hrs after acquisition ($p=0.0066$) or expression testing ($p=0.012$) animals that displayed more freezing to tones had higher DCX than low-freezing animals. High-DCX animals also displayed a greater tendency to associate unpaired tones with shocks ($p=0.003$) and to generalize freezing to novel tones ($p<0.0001$). Analyses of RNA from brain and blood further revealed multiple genes whose expression in blood 2hrs post-fear learning were correlated with both AMY DCX RNA and with the extent of freezing displayed during fear acquisition ($p<0.005$) and expression testing ($p<0.01$). Conclusions: Individual differences in fear

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acquisition, expression, and generalization are reflected in subsequent changes in the expression of amygdala DCX and plasticity-related genes in blood.

3-F-185 *Challenging physical activity enhances resilience-like behaviours and females show more resilience-like behaviors*

Stephanie Dudok[1], Sarah Curtis[1], Tammy Ivanco[1]

[1]University of Manitoba

Physical activity plays a role in inducing plastic changes in the brain to enhance resilience to stress and anxiety, however, there has been limited investigation as to whether the quality of activity matters. The present study examined whether participation in cognitively-demanding physical activity promotes resilience to anxiety, compared with participation in regular or no physical activity. Thirty-six Long-Evans rats were randomly assigned to one of three experimental conditions over four weeks: A- physical activity, B- cognitively-demanding physical activity, and C- sedentary. Subjects in Group A ran in cage wheels for 30 min/day increasing to 60 min/day. Subjects in Group B performed a complex motor task for 20 trials/day followed by 30min/day of wheel running. Sedentary subjects did not participate in any physical activity. All subjects underwent three behavioral tests designed to elicit anxiety-like responses. Subjects in Group A displayed less feeding suppression in the novelty-suppressed feeding test and this relationship was moderated by sex. Subjects in Group B displayed fewer anxiety-like behaviors compared to sedentary controls in the elevated plus maze, entering more frequently into open arms. Female subjects displayed fewer anxiety-like behaviors than males in the light-dark box whether or not they were physically active. These findings demonstrate physical activity does enhance resilience to the behavioral consequences of stress and anxiety, and that resilience is greater when the activity is enriched with cognitive elements.

3-F-186 *Perineuronal net maturation around parvalbumin interneurons underlie the emergence of memory specificity*

Bi-ru Amy Yeung[1], Adam Ramsaran[1], Moriam Ahmed[1], Sheena Josselyn[1], Paul Frankland[1]

[1]University of Toronto

Across species, memory in infants is characterized by profound generalization, with memory specificity emerging during childhood. We hypothesized developmental factors regulating neural plasticity may underlie the ontogeny of memory specificity, investigating the role of perineuronal nets (PNNs) regulating the development of memory specificity. Using contextual fear conditioning in developing mice, we show memory specificity emerging between postnatal days (P) 20 and 24,

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at the same time PNNs in CA1 reach adult levels. We further demonstrated a causal relationship between CA1 PNN accumulation and memory specificity, by pharmacologically degrading and accelerating PNN growth in adult and infant mice respectively. Adults displayed infant- like generalization, while infants demonstrated adult-like memory specificity, indicating PNN maturation in the hippocampus is necessary and sufficient for the emergence of memory specificity during postnatal development. Recognizing CA1 PNNs preferentially ensheath PV interneurons, and PNN proteins are expressed in an activity-dependent and cell-autonomous manner, we also asked whether activity of PV interneurons was necessary for PNN integrity and memory specificity. Chronic inhibition of CA1 PV internerneuron activity in PV-Cre transgenic mice, via designer receptor hM4Di activation, decreased PNN density, suggesting that activity is necessary for maintenance of PNN integrity. Overall, the emergence of memory specificity is affected by hippocampal PNN development, which can be indirectly regulated through PV interneuron activity.

3-F-187 *Occasion setting with interoceptive drug states: morphine's role as a positive and negative feature and its impact on motivational behaviour*

Allyson Andrade[1], Briana Renda[1], Karlie Lambert[1], Cassandra Sgarbossa[1], Jennifer Murray[1]

[1]University of Guelph

Drugs of abuse evoke interoceptive stimuli that can guide appetitive behaviour. How such an appetitive learning history affects reinforcement value is largely unknown. Thus, this research investigated the impact of training morphine as a feature positive (FP) occasion setter (OS), indicating a white noise (WN) conditioned stimulus (CS) will be followed by sucrose unconditioned stimulus, on subsequent morphine self-administration. We hypothesized that rats with an appetitive learning history (FP) will have greater motivation to return to that interoceptive state than rats with a non-appetitive learning history in which morphine is a feature negative (FN). 20 male Sprague-Dawley rats were assigned to FP or FN training. All rats were given daily intermixed morphine or saline sessions containing eight 15-sec WN presentations. For FP rats, on morphine sessions, each WN offset was followed by access to sucrose; on saline sessions, no sucrose was available. For FN rats, sucrose was delivered on saline sessions and withheld on morphine sessions. Both groups learned to discriminate morphine from saline. Rats then underwent jugular catheterization and entered self-administration. For 16 sessions rats were on a fixed ratio 1 schedule, then moved to a fixed interval 1 schedule. There were no differences in total infusions or active lever presses between FN and FP. Thus, differential conditioned experiences did not influence motivational values of the morphine OS. This finding may be dependent on the associative architecture; future research will train morphine as a direct CS.

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3-F-188 *Assessing self-recognition in mice*

Angela Fung[1], Jesse Jackson[1]

[1]University of Alberta

Prosocial animals possess a high level of emotional intelligence, which enables the ability to form meaningful relationships with others. Self-concept is thought to be an essential cognitive function that drives social interaction, though the neuroanatomical mechanisms for this phenomenon remain unclear. Mice are highly social animals yet there is little data investigating if mice are capable of self-recognition. To test if mice are capable of self-recognition, we have modified traditional mirror self-recognition (MSR) tasks and applied them to study mice. Our protocol requires several consecutive days of training, where the mouse has the opportunity to explore the front and back of a mirror. We have assessed MSR in C57Bl/6 mice which were trained with or without exposure to a mirror rich environment. Following habituation and training, a visible mark was placed on the animal while under brief anesthesia and the mouse placed in a novel mirror environment for behavioural analysis. When the mouse recovered from anesthesia, we quantified the location and duration of grooming bouts, directed toward the visible marking, for mirror training and untrained mice. Our preliminary data suggests that mice are capable of identifying themselves in the MSR task, in an experience dependent manner. Future work will identify the neural circuits that underlie self-recognition behaviour.

3-F-189 *Developmental stage-specific effects of alcohol can be detected in larval, 6-8 day old, zebrafish.*

Amira Abozaid[1], Zelaikha Najmi*[1], Lidia Trzuskot*[1], Ishti Paul[1], Benjamin Tsang[2], Robert Gerlai[2]

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

Despite the known deleterious effects of alcohol, Fetal Alcohol Spectrum Disorder (FASD) remains prevalent worldwide because of alcohol consumption by pregnant women. The severity and symptoms of FASD show high variability across affected children. One possibility for this variance is consumption of alcohol at different stages of pregnancy. Another is the genotype of the fetus. Zebrafish allows precise dosing and timing of alcohol delivery during embryonic development. We investigated how embryonic alcohol administration affected behavior in two different zebrafish strains, AB and WT. To examine the possible differential effects of timing of alcohol exposure during embryonic development, we immersed zebrafish embryos into 1% ethanol solution or freshwater (control) for 2 hours at 8 hours post fertilization (hpf), 16 hpf, 24 hpf, 32 hpf, or 40 hpf. Subsequently, we returned the embryos to their holding tank and allowed them to develop normally. At 6-8 days post fertilization (dpf) age, we tested the behavior of each

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fish singly in an open 3.5 mm diameter circular well during a 30-minute session, quantifying their swim path parameters. Our results show that alcohol's effects were dependent upon the developmental stage and strain, i.e. we found significant genotype x alcohol treatment interaction in frequency and duration of immobility, frequency and duration of thigmotaxis as well as in total distance travelled. Our results demonstrate, for the first time, that zebrafish can be used to detect embryonic alcohol effects as early as at their age of 1 week post fertilization.

3-F-190 *Varenicline treatment dose-dependently increases ethanol self-administration in sprague-dawley rats*

Briana Renda[1], Allyson Andrade[1], Joshua Smit[1], Lauren King[1], Jibran Khokhar[1], Scott Barrett[1], Jennifer Murray[1]

[1]University of Guelph

Objective Varenicline is an effective prescription pharmacotherapy for smoking cessation. A recent study found evidence that varenicline can also dose-dependently decrease ethanol consumption in alcohol-preferring rats. The effect of varenicline treatment on ethanol consumption in rats with lower baseline consumption is not known. Method 19 Sprague-Dawley rats underwent a sucrose fading procedure where they learned to lever press for the presentation of 0.01 ml of 15% ethanol, then maintained on a fixed ratio 1 (FR1) schedule of reinforcement. Next, we assessed the effect of varying doses of varenicline pretreatment (0, 0.3, 1, and 3 mg/kg, s.c.) on ethanol consumption across increasing fixed-ratio schedules (FR1, FR2, FR5, FR10, FR15). Each FR schedule consists of 11 daily sessions of varenicline or vehicle (saline) pretreatment 15 min prior to a 50 min self-administration session. The first two days of each schedule are baseline saline days, followed by eight days of treatment with each rat exposed to all the doses in two unique orders, and one final saline day. Results Varenicline pretreatment dose-dependently increases ethanol consumption in Sprague-Dawley rats such that lower doses increase ethanol consumption whereas a high dose does not. Conclusion Varenicline dose-dependently enhances ethanol self-administration in a low-drinking strain of rat. Varenicline may exert diverse effects on ethanol self-administration based on different baseline consumption levels.

3-F-191 *Differential effects of intra-PFC tetrahydrocannabinol and cannabidiol on approach-avoidance and latent inhibition in rats.*

Tony Jung[1], Hanna Szkudlarek[2], Roger Hudson[2], Marta De Felice[2], Steven Laviolette[2], Walter Rushlow[2]

[1]Western University, [2]University of Western Ontario

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The prefrontal cortex (PFC) regulates multiple psychological processes including anxiety and cognition, and it plays a critical role in the development of various psychiatric disorders. Chronic cannabis use is linked with the development of schizophrenia-like symptoms and cannabinoids exposure in healthy volunteers may induce schizophrenia-like symptoms. The cannabis plant produces multiple phytochemicals with tetrahydrocannabinol (THC) and cannabidiol (CBD) being the most abundant. While systemic THC induces psychotomimetic symptoms, CBD is devoid of such actions and may counter THC's effects if co-applied. Clinical and pre-clinical evidence demonstrates that CBD possesses anti-psychotic and anxiolytic properties. However, it is unknown if the beneficial properties of CBD extend to the otherwise healthy brain state, or are limited to pathological neuropsychiatric conditions. Here we tested the acute effects of intra-PFC THC and CBD, using behavioral and molecular approaches. We show that THC exerts panic-like responses in the elevated T-maze that can be blocked by the co-application of CBD. In contrast, CBD alone did not affect behavior in the T-maze test, while it greatly impaired latent inhibition and perception of animals tested with auditory fear conditioning paradigm and simultaneous oddity discrimination task respectively. Moreover, CBD induced molecular changes in GSK and JNK pathways. CBD's effects were prevented with co-application of a 5-HT1A antagonist (NAD) suggesting that CBD affects local PFC circuitry by acting through a serotonergic transmission mechanism.

3-F-192 *Psychopathic traits and substance use associated with multimodal disruptions of rest-related neural activity in offenders*

Isabelle Simard[1], Matthew Shane[1]

[1]University of Ontario Institute of Technology

Offender populations often present with heightened levels of substance use and psychopathic traits, as well as with neural network dynamics disruptions. Previous accounts reported that psychopathic traits and drug use contribute to these neural disruptions, however, the extent of this contribution is still unknown. Thus, we investigated the contribution of psychopathic traits (measured via the PCL-R), Lifetime Substance Use (LSU), and their interaction on 3 modalities of rest-related brain activity (BOLD activity, Power Spectra (PS) and Functional Connectivity (FNC)) in 84 male offenders. Through ICA analysis in GIFT, neural networks were classified into 34 BOLD-related components. Psychopathic traits were associated with decreased BOLD activity in the cingulate gyrus. LSU reflected decreased BOLD activity and PS in the precuneus, as well as PS disruptions in the superior parietal lobule. An interaction between PCL-R scores and LSU related to a decreased BOLD activity in the superior temporal gyrus. Separating total drug use into 'major drugs' (e.g. cocaine/opioids/meth) and 'minor drugs' (e.g. cannabis/nicotine) indicated that major drug use was more related to disruptions in BOLD activity, while minor drugs were more related to spectral and FNC differences. These results suggest that psychopathic traits and LSU

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differently affect brain activity in offenders, with psychopathic traits and major drug use relating to disruptions in BOLD activity and minor drug use to alterations in PS and FNC, providing potential neural markers of offending behaviour and treatment targets.

3-F-193 *Dysfunction of the orbitofrontal cortex in diet-induced obesity*

Lindsay Naef[1], Lauren Seabrook[1], Corey Baimel[2], Stephanie Borgland[1]

[1]University of Calgary, [2]New York University

The lateral orbitofrontal cortex (lOFC) is involved in the cognitive control of reward processing. It keeps information online and updates behaviour based on changing reward contingencies. Human studies have demonstrated that obesity is associated with lower behavioural adaptation to reward devaluation. The goal of the present experiments was to test the hypothesis that the lOFC is impaired in an animal model of diet-induced obesity associated with altered reward devaluation. We show that that obesity shifts reward, making obese animals insensitive to devaluation by satiety, conditioned taste aversion and by a switch in the prevailing relationship between lever pressing and reward delivery. Using patch-clamp electrophysiology, we show that obesity decreases inhibitory tone and thus, increases the excitability of orbitofrontal cortex output neurons. To directly link these synaptic changes and behaviour, we target inhibitory neurons of the orbitofrontal cortex using chemogenetics. We show that interneurons are necessary for determining the firing rate of output neurons and for performance in reward devaluation tasks.

3-F-195 *Prediabetes accelerates age-related neurocognitive decline*

Joyla Furlano[1]

[1]Western University

Type II diabetes (T2D) is associated with cognitive and neural decline beyond normative aging, and thus older adults with T2D are at very high risk for developing dementia. However, the extent to which similar deficits occur in prediabetic older adults are currently unknown. While some studies have shown that prediabetic older adults experience some cognitive decline, further research is needed to determine the specific cognitive domains affected and the degree to which this decline occurs. Moreover, structural and functional brain changes that may occur with these deficits is unknown in this population. Therefore, the aim of this study was to assess cognitive performance and brain health in prediabetic older adults. We conducted a cross-sectional analysis of older adults (aged 60-80) with prediabetes (fasting plasma glucose 6.1-7.0 mmol/L) and healthy aged-matched controls, examining 1) memory performance using the Digit Span, RAVLT, and ADAS-Cog, 2) functional brain activation of the hippocampus as measured by fMRI during an

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associative memory task, and 3) high resolution T1 weighted structural images to assess hippocampal volume. Based on our cross-sectional analysis, prediabetic older adults do show impaired memory performance compared to healthy controls, as well as decreased hippocampal volume and activation. Therefore, we conclude that older adults with prediabetes experience cognitive and brain decline, and could benefit from lifestyle interventions to prevent or delay the onset of such decline.

3-F-196 *The effect of navigational strategy on theta activity while playing a platform video game.*

Hugo Laflamme[1], Simon Rigoulot[2], Karim Jerbi[1], Sarah Lippé[1], Greg West[1]

[1]Université de Montréal, [2]Université du Québec à Trois-Rivières

As it must orientate itself in the environment, the human being spontaneously uses navigational strategies to arrive to its destination. These strategies can be either "spatial" or "response", depending upon which structure among the hippocampus or the caudate nucleus has the most predominant volume. As the spatial strategies are associated to a higher grey matter volume in the hippocampus, the response strategies are related to a lower volume. The aim of this study is to demonstrate that platform video games allows to stimulate a significant amount of hippocampic activity that can be recorded through EEG. Behavioral tasks have been administered to the subjects to assess their strategy. The subjects were split in two experimental groups: spatial and response learners. We monitored the theta frequential activity (4-8Hz) (as we know it to be linked to hippocampic activity) as well as gamma wavebands (30-50Hz) while they played a platform video game. While we estimate that there should be a significant augmentation of theta activity on both groups, it should be more important among the subjects using instinctively a spatial strategy. Our results demonstrate that spatial learners show a theta activity augmentation in all analyzed scalp region (frontal, central, parietal, occipital), while response learners only show a significant augmentation in the frontal region. These results show that platform games might be used to stimulate theta activity that may be recorded through EEG. Further studies based on this protocol would be required to locate the source(s) of this activity.

3-F-197 *The facilitating role of oxytocin on sexually conditioned partner preference in female rats.*

Eamonn Gomez-Perales[1], Conall Mac Cionnaith[1], Marjolaine Rivest-Beauregard[1], Rebecca Cernik[1], Alice Lemay[1], Wayne Brake[1], Andrew Chapman[1], James Pfaus[2]

[1]Concordia University, [2]Universidad Veracruzana

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Female rats form conditioned sexual partner preferences when they are given repeated paced copulatory trials with almond scented males. When given a final choice test, such females solicit and copulate preferentially with scented over unscented males. Because research on prairie voles has shown that systemic administration of oxytocin facilitates the acquisition of monogamous partner preferences, we asked in the present study whether oxytocin could facilitate conditioned partner preferences in female rats. Ovariectomized, sexually naïve females (N=72) were hormonally primed with estradiol benzoate and progesterone and given 1, 5, or 10 sexual conditioning trials with almond-scented males. Prior to each trial, half of the females in each group were treated with intraperitoneal injections of either oxytocin (20µg/.2ml) or an equal volume of saline. A final open field test was given to the three groups in which each female was allowed free access to two tethered, sexually vigorous males, one scented with almond and the other unscented, and her sexual behaviors with each male were scored. Preliminary results show no formation of conditioned partner preference in the 1-trial group with 45% of females in the oxytocin group receiving their first ejaculation from a scented male and 50% in the saline group. We are currently completing the 5-trial and 10-trial groups which will allow us to determine how administration of oxytocin is affecting the rate of acquisition of conditioned partner preference.

3-F-198 *The posterior parietal cortex modulates sound-evoked responses in the auditory cortex*

Michael Kyweriga[1], Navvab Afrashteh[1], Edgar Bermudez-Contreras[1], Jianjun Sun[1], Artur Luczak[1], Majid Mohajerani[1]

[1]Lethbridge University

The posterior parietal cortex (PPC) is a multi-modal sensory association area sharing reciprocal connections with the auditory cortex (AC) and appears to be involved in decision-making. Based on this background, we wondered whether the PPC might serve in a modulatory role over the AC. First, we show for the first-time electrophysiological maps of sound-evoked responses in the isoflurane-anesthetized mouse PPC. This was our most surprising result given that all previous research showing electrophysiological responses in the PPC was during awake auditory decision tasks. Our results suggest that the PPC is involved in basic sensory processing of auditory information. Second, we implanted fiber optic ferrules to deliver light in vivo to the auditory-PPC of mice expressing channelrhodopsin-2 in either excitatory or inhibitory neurons. We discovered that stimulation, but not inhibition, of the PPC led to a significant reduction of performance in an operant tone-discrimination task. Third, we performed electrophysiology recordings in the AC of isoflurane-anesthetized mice with fiber optic implants over their auditory-PPC. We found that stimulation, but not inhibition, of the PPC caused significant reduction to the onset response to pure tones in the auditory cortex. Together, these results provide evidence that the PPC is poised to both receive direct auditory stimulation and that it can exert top-down modulation of the

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auditory cortex during acoustic sensory processing. Our future work plans to investigate the role of the PPC in hearing disorders, such as tinnitus.

3-F-199 *Odour engrams are stored in the anterior olfactory nucleus*

Afif Aqrabawi[1], Junchul Kim[1]

[1]University of Toronto

The anterior olfactory nucleus (AON) is the initial recipient of odour information from the olfactory bulb, and the target of dense innervation conveying spatiotemporal cues from the hippocampus. We hypothesized that the AON detects the coincidence of these inputs, generating patterns of activity reflective of episodic odour engrams. Using activity-dependent tagging and genetic manipulation techniques, we reveal that odour-specific engrams are stored within the AON and that their activity is both necessary and sufficient for the behavioural expression of odour memory. Our findings offer a new model for studying the mechanisms underlying memory representations.

3-F-200 *Recruitment of thalamic spindle-generating circuitry promotes EEG patterns of general anesthesia, but does not alter general anesthetic-induced loss-of-consciousness*

Lia Mesbah-Oskui[1], Patrick Gurges[2], Wenying Liu[2], Richard Horner[2]

[1]Queen's University, [2]University of Toronto

Alterations in thalamic GABAergic signaling are implicated in mediating the rise in 12-30Hz EEG activity that signals anesthetic loss-of-consciousness (LOC) with GABAAR-targeting anesthetics. We hypothesize that recruitment of this thalamic GABAergic circuitry into a sleep-spindle mode of activity promotes the anesthetic effects of etomidate. We recorded EEG activity and loss-of-righting reflex (LORR) in freely behaving WT and transgenic mice expressing channel rhodopsin-2 receptors on GABAergic cells (ChR2-VGAT). All mice were instrumented with EEG and EMG electrodes and a unilateral optic probe targeting the left reticular thalamic nucleus. Experiments occurred over 2 days where mice were randomly assigned to receive optogenetic stimulation on one day and no stimulation on the other. After an initial 30min, mice received a bolus IP dose of etomidate and were recorded for 90min with or without stimulation. Etomidate elicited increased 12-30Hz power in the first 20min in both WT and ChR2-VGAT mice. Optogenetic stimulation prolonged the increase in 12-30Hz activity in ChR2-VGAT mice. Optogenetic stimulation increased the incidence and duration of sleep spindle-like oscillations in ChR2-VGAT mice. Despite the anesthetic-like changes in the EEG, optogenetic stimulation did not change LORR. This study identifies that recruitment of thalamic spindle circuitry during anesthesia promotes

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anesthetic LOC-like EEG changes. Despite these changes LORR was unaffected, indicating that unilateral recruitment of this circuitry during anesthesia is insufficient in maintaining LOC.

3-F-201 *Effects of cognitive load on cortical oscillations during a pattern learning task using MEG and pupillometry*

Silvia Isabella[1], Douglas Cheyne[2]

[1]University of Toronto and Hospital for Sick Children, [2]University of Toronto and The Hospital for Sick Children (SickKids)

Although studies involving use of cognitive control demonstrate changes in brain activity, the functional roles of these signals remain unknown. The objective of this study is to characterize cortical oscillations related to increases in cognitive and motor demands. We hypothesize that frontal θ and sensorimotor γ power will increase with cognitive effort (speed + load) required by the task (as measured by reaction time, RT, and pupil diameter, PD) while post-movement β rebound (PMBR) will decrease with effort. We measured neuromagnetic (MEG) brain activity in 16 right-handed healthy adults performing 6 blocks of a go/switch task (Switch=25%). We manipulated stimulus predictability using fixed stimulus sequences (P=90%, d=10%) that were unknown to the participants. There was a main effect of response hand (Go/Switch) and pattern (all $p<0.01$) on RT and PD. Given that PD was more sensitive than RT to the task parameters, subjects likely increased cognitive load (PD) to reduce differences in performance (RT). We found that θ activity was more sensitive to the pattern ($p<0.001$) than to the Switch response ($p<0.02$), indicating a role in surprise detection. Furthermore, PMBR and γ increased with cognitive load, but did not correlate with RT or PD, indicating a role in integrating cognitive and motor parameters together. This study is the first to distinguish these roles for these cortical oscillations, while demonstrating a role for frontal activity in surprise detection over cognitive control, and a role for sensorimotor activity in integrating cognitive and motor control.

3-F-202 *Specific firing patterns of VTA GABA neurons encode the motivational experience of acute opiate reward*

Lyla El-Fayomi[1], Michael Bergamini[1], Hendrik Steenland[2], Geith Maal-Bared[1], Derek van der Kooy[1]

[1]University of Toronto, [2]NeuroTek

Opiate addiction is a debilitating and costly disease. Previous experiments in our lab have shown that the "rewarding" effect of opiates in drug-naïve animals is mediated by GABA neurons of the

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ventral tegmental area (VTA). This effect is independent of dopamine, as morphine conditioned place preferences (CPPs) in drug-naïve mice are resistant to D1/D2 receptor antagonism. We now propose that opiate reward in drug-naïve mice cannot be encoded in on-off models of neural communication, but rather, in specific firing patterns. This may reconcile seemingly conflicting data; chemical and genetic experiments support a role for VTA GABA neurons in naïve reward, but optogenetic stimulation drives aversion. GABAa receptor agonism and antagonism on VTA GABA neurons results in reward behaviour. Also, in B2 receptor subunit knockout mice, nicotine CPPs are restored only when B2 is rescued in VTA GABA neurons. These findings contrast work by Tan et al. demonstrating that optogenetic 20 Hz stimulation is aversive. As non-patterned 20 Hz stimulation is not physiologically relevant, it may produce a negative punishment effect, wherein baseline signalling in the VTA (potentially signalling safety or comfort) is disturbed. We investigated this by collecting in vivo electrophysiological recordings of VTA GABA neurons from mice under the influence of morphine. We then played those firing patterns back to VTA GABA neurons using optogenetics. We observed statistically significant, real-time CPPs for this stimulation, supporting the pattern hypothesis of naïve opiate-related reward motivation.

3-F-203 *Lifespan changes in regional brain volume and cognitive performance associated with normal aging in mice*

Amy Miles[1], Keith Misquitta[1], Thomas Prevot[1], Jacob Ellegood[2], Jason Lerch[2], Etienne Sibille[1], Yuliya Nikolova[1], Mounira Banasr[1]

[1]CAMH, [2]Hospital for Sick Children

Normal aging is associated with changes in brain volume that span maturational and degenerative processes, paralleled by changes in cognitive function. In order to further characterize these changes, we collected behavioural and structural MRI data from young mice (2 months, n=10), middle-aged mice (12 months, n=10), and old mice (22 months, n=9). Volume of atlas-based parcellations (n=182) was measured with deformation-based morphometry, and dimension reduction, yielding 30 regions, was performed with hierarchical clustering. Working memory was measured using the Y-maze test. Analyses of variance identified significant group differences in volume in more than half of the regions tested (n=19/30, $p<0.05$). Consistent with previous studies, we found that volume of subcortical nuclei and white matter tracts increased from early to mid-life, and volume of cortical areas decreased from early to mid-life, and, in some cases, into late life. Logistic regression analyses revealed significant positive associations between volume in several of these regions, including the striatum and anterior cingulate cortex, and cognitive performance ($\chi 2$ = 4.0, 5.4, respectively; $p<0.05$), suggesting a link between aging, cellular remodeling, and cognitive decline. We are currently testing mediation models thereof, and we are examining patterns of structural connectivity in regions of interest. Ultimately, we aim to identify

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robust structural signatures of normal and pathological brain aging, which may improve current models of age-related disorders and facilitate translation to human studies.

3-F-204 *Intra-individual variability in reaction time: A robust marker of sex differences in prefrontal cortex (PFC) - based tasks*

Varsha Singh[1], Vaishali Mutreja[1]

[1]Indian Institute of Technology, Delhi

Introduction: Intra-individual variability (IIV) in reaction time (RT) was used to delineate sex-differences in executive functions (working memory, inhibition, flexibility and decision-making) because evidence for sex-differences in prefrontal cortex (PFC)-based functions is inconclusive. Method: Healthy student volunteers (N=183, mean=22. 39 yrs.) performed tasks (digit span task, Simon task, Tower of Hanoi, & Iowa gambling task). Transformed mean and IIV RT (SD/Mean RT) was analyzed separately for males (n=149) and females (n=34) using correlation. Analysis and results: In females, working memory mean RT positively correlated with that of inhibition (r = .39; p = .02). In males, working memory mean RT positively correlated with that of decision-making (r = .17; p = .04), inhibition mean RT positively correlated with that of flexibility (r = .24; p = .00), and decision-making (r = .21; p = .00). When IIV RT were used, working memory IIV RT positively correlated with that of inhibition (r = .63; p = .00) for females; males showed no significant correlations in IIV RT of the four tasks. Conclusion: Working memory and inhibitory control in females has common intra-individual variability in RT; but RT variability in four PFC-based functions remained uncorrelated in males. Variability rather than average RT might be more robust marker of sex differences, possibly indicative of degree integration in PFC-based functions.

G - Novel methods and technology development

3-G-205 *Can operant discrimination of acoustic stimuli increase neurogenesis in auditory perceptual brain regions in zebra finches (Taeniopygia guttata)?*

Sean Aitken[1], Sean Aitken[1], Adana Crabbe[1], Leslie Phillmore[1]

[1]Dalhousie University

In adult songbirds such as the zebra finch (Taeniopygia guttata), neurons are born in the subventricular zone and migrate to many brain regions including those important for auditory perception, such as HVC and NCM. In birds and mammals, engaging in cognitively demanding tasks can increase neurogenesis in the hippocampus compared to subjects who do not engage in the tasks, but it is unclear whether this effect extends to auditory discrimination tasks and their associated brain regions. To study this, we injected birds with the cell birth-marker

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bromodeoxyuridine (BrdU) and then divided them into three groups. Birds in one group were exposed to a difficult operant task where they attempted to discriminate between patterns of three-note sequences for a food reward. In a second group, each bird was housed in an adjacent operant chamber connected to a bird in the discrimination group and heard everything played to that bird in real time, but was not required to work for food. Birds in a third control group heard no stimuli. After three weeks, we harvested their brains and labeled for BrdU and the immediate-early gene ZENK using immunohistochemistry. If performing a cognitively demanding task promotes neurogenesis, we expect the number of BrdU and ZENK co-labeled cells in HVC, NCM and hippocampus to be higher in discrimination birds compared to yoked-control and control birds. Findings from our study will be useful in evaluating the effectiveness of cognitively challenging tasks to increase neurogenesis and to mitigate or prevent neurodegeneration.

3-G-206 *DeepEEG: A Keras/TensorFlow library and notebooks for machine learning with neurophysiological data*

Kyle Mathewson[1], Kory Mathewson[1]

[1]University of Alberta

We introduce DeepEEG, an open-source, collaborative Python library for machine learning applied to electrophysiological data using Google Tensorflow/Keras along with the MNE toolbox. We present a series of network architectures as well as their implementation in readable, runnable code examples, and show strategies for preparing EEG data for input to these models. We discuss alternatives and considerations in engineering of features from the ongoing time series data. We show examples of single layer, deep, convolutional, recurrent, and autoencoding neural networks and present basic use cases as starting points. We present current best practices for neural network design, training, validation, and testing. Currently no other libraries or frameworks exist most researchers roll-their-own analysis. We provide open-source code and easy to use, browser based examples and sample data to reduce the time and effort needed to start writing research code. We hope that the DeepEEG library (https://github.com/kylemath/DeepEEG) will be a launch pad toward accelerating research in this exciting data analytic application.

3-G-207 *Capturing the forest but missing the trees: Microstates inadequate for characterizing shorter-scale EEG dynamics*

Saurabh Shaw[1], Kiret Dhindsa[1], James Reilly[1], Suzanna Becker[1]

[1]McMaster University

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The brain is known to be active even when not performing any overt cognitive tasks, and often engages in involuntary mind wandering. This resting state of the brain has been extensively characterized using fMRI-derived brain networks. However, an alternate method has recently gained popularity - EEG microstate analysis. Proponents of microstates postulate that the brain discontinuously switches between four quasi-stable states defined by specific EEG scalp topologies at peaks in the global field potential (GFP). These microstates are thought to be "atoms of thought", involved with visual, auditory, salience and attention processing. However, this method makes some major assumptions by excluding EEG data outside the GFP peaks and then clustering the EEG scalp topologies, assuming that only one microstate is active at any given time. This study explores the evidence surrounding these assumptions by studying the temporal dynamics of microstates and its clustering space to highlight the shortcomings in microstate analysis. The results show complex and chaotic EEG dynamics outside the GFP peaks, which is missed by microstate analyses. Furthermore, the winner-takes-all microstate approach is found to be inadequate since there is dynamic competition between the different microstate classes. Finally, clustering space analysis shows that the four microstates do not cluster into four distinct and separable clusters. Taken collectively, these results show that the discontinuous description of microstates might be inadequate when looking at non-stationary short-scale EEG dynamics.

3-G-208 *Identification of novel regulators to mediate alternative splicing of Tau exon 10*

Sansi Xing[1], Jane Wang[1], Kaiyuan Wang[1], John Crary[2], Yu Lu[1]

[1]McMaster University, [2]Ronald M. Loeb Center for Alzheimer's Disease Icahn School of Medicine at Mount Sinai

Tauopathies are defined by a set of sporadic and familial neurodegenerative diseases, which are characterized by aggregates of microtubule-associated protein Tau. One contributing factor to tauopathy is deregulated Tau alternative splicing. Tau exon 10 encodes the second microtubule-binding repeat and its alternative splicing (AS) produces three or four microtubule-binding repeats, termed 3R-Tau or 4R-Tau. Whereas equal amount of 3R- and 4R-Tau are found in neurotypically normal adult human brain, distorted 3R/4R Tau ratio is associated with tauopathy. The mechanism that contribute to aberrant Tau exon 10 AS and sporadic tauopathy pathogenesis remains elusive, which is crucial knowledge to develop treatment for these neurodegenerative diseases. RNA antisense purification by mass spectrometry (RAP-MS) was recently published for protein-RNA interaction studies. To date there has been no report applying RAP-MS to investigate alternative splicing regulation. In this study, we proposed to unitize RAP-MS to study Tau splicing. With 31 antisense probes we successfully captured Tau primary mRNA and identified 64 RNA-binding proteins (RBPs) that bound to Tau primary mRNA (including 12 known Tau exon 10 AS regulators) through mass spectrometry. We knocked down the top 14 RBPs individually and found that HNRNPK, HNRNPC, HNRNPU, HNRNPA2B1 support 4R-Tau expression whereas LUC7L3

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mediates 3R-Tau expression. With future validation in animal models and patient studies, these novel Tau exon 10 AS regulators may represent potential drug targets for tauopathy therapeutics development.

3-G-209 *Predicting seizure onsets using cross-frequency coupling features and deep learning*

Christopher Lucasius[1], Berj Bardakjian[1]

[1]University of Toronto

Over 15 million people are resistant to drugs that treat epilepsy, leading to a need for seizure detection systems. Traditionally, neuroscientists have sifted through electroencephalogram (EEG) data to discern which signals correspond to seizures, and which do not. This is typically very time-intensive, which is why novel approaches involving feature extraction and machine learning for classification are drawing a significant amount of attention. One feature that has been shown to correspond well to seizure activity is the cross-frequency coupling index (CFC), which is an image representing the modulation between high and low frequency components of an EEG signal in a specific time window. In my presentation, I intend to demonstrate using CFC images as inputs into a deep neural network (DNN) for classification of seizure states. These networks have proven to be quite effective in classifying images accurately and specifically, justifying why DNNs should be used in analyzing EEG images. Previous machine learning methods have also been applied directly to EEG data, and while they proved to be very accurate, many still struggled to reduce false positives in their predictions. By training the DNN over several epochs of EEG data of multiple epileptic patients, the specificity is expected to increase significantly compared to other classifiers. Recently, CFC images have shown to be not only effective in identifying seizure activity in adults, but also in children. Hence, the DNN is trained on both adult and pediatric datasets to create a general classifier for seizure detection.

3-G-210 *Optogenetic control of cAMP and cGMP from single synapses to brain subregions*

Megan Valencia[1], Kenichi Okamoto[1]

[1]Lunenfeld-Tanenbaum Research Institute

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are intracellular second messengers critical for a variety of physiological functions such as synaptic plasticity and learning/memory. The enzymes adenylyl/guanylyl cyclases (AC/GC) and phosphodiesterases (PDEs) regulate levels of cAMP/cGMP and serve as drug targets for

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neuropsychiatric disorders such as Alzheimer's disease. Pharmacological reagents and genetic manipulations have been utilized to address their functions, however, these approaches have limited spatiotemporal specificity. Here we introduce the systematic application of photoactivatable enzymes to manipulate cAMP/cGMP by light at single synapses and living hippocampal neurons. To photoactivate the enzymes at the synapse, we utilized two-photon focal light excitation. After two-photon characterization of photoactivatable enzymes in vitro, we co-expressed these enzymes with genetically-encoded cAMP/cGMP fluorescence sensors in CA1 pyramidal neurons of living hippocampal slices. We observed dynamic changes of cAMP/cGMP levels after two-photon light illumination, demonstrating two-photon light-dependent photoactivation of these enzymes in live neurons. Furthermore, we stereotaxically microinjected optogenetically-encoded viral particles into the hippocampal regions of the mouse brain and will discuss the application of these photoactivatable enzymes at the animal behaviour level. Thus, our established optogenetic approach provides powerful tools to address spatiotemporal cAMP/cGMP functions in an unprecedented way.

3-G-211 *Spike sorting of high-density multielectrode arrays: identification of excitatory and inhibitory units in large-scale neuronal circuits*

Eloïse Giraud[1], Jean-Claude Beique[1], Jean-Philippe Thivierge[1]

[1]University of Ottawa

Large-scale extracellular recordings are a valuable tool for investigating the activity of thousands of neurons simultaneously, but the volume and complexity of data obtained makes spike sorting computationally challenging. Here, we introduce a method for the analysis of large-scale recordings of in vitro cortical activity and offer tools for automated unit selection and quality control. The proposed approach fits individual spike waveforms using a spline interpolation in order to estimate their half-amplitude and peak-to-peak durations. These values are then entered in a principal component analysis with k-means clustering to identify uncorrelated signals from single channels on the array. Optimal separability of clusters is assessed by linear discriminant analysis. Finally, each channel's source location is identified using spatiotemporal characteristics of spike waveforms across the array. We validated this method using spontaneous activity monitored with an array of 4,096 closely-spaced channels. We show an effective distinction of regular-spiking excitatory neurons from fast-spiking inhibitory interneurons using measures of firing rates, inter-spike intervals, Fano factor, pairwise correlations and spatially-dependent correlations. In sum, the proposed approach allows for a comprehensive characterization of neuronal activity obtained from high-density multielectrode recordings. This provides a platform to investigate the interplay of excitation and inhibition in microcircuits of the brain.

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3-G-212 *Use of the MLSpike algorithm in the analysis of neuron network structure in the zebrafish larva*

Jean-Christophe Rondy-Turcotte[1]

[1]Université Laval

The analysis of neuron networks necessitates information on how neurons are connected to each other. The difficulty of directly observing the physical connection between neurons leads to the strategy of using statistical analysis of neural activity patterns to infer the most likely connections. Calcium imaging of zebrafish larvae gives research teams a lab animal in which it is possible to observe neuron activity, as the animal is transparent. However, recovering the precise timing at which each neuron fires action potential by analysing variations in fluorescence is a computationally difficult task. This presentation details the challenges and potential rewards of better methods to extract precise timing of neuron activity, and presents one approach in details. Based on the work of Deneux et al., this method uses hidden states Markov chains and the Viterbi algorithm to extract spiking activity from the noisy fluorescence data in a computationally efficient way. The performance of this method is compared to methods that came before and after it, and its impact on the conversion of raw fluorescence data obtained in the lab into information on the structures of neural networks is discussed.

3-G-213 *Measuring the effects of mean arterial pressure changes on spinal cord hemodynamics in a porcine model of acute spinal cord injury using a novel optical technique*

Amanda Cheung[1], Babak Shadgan[1], Neda Manouchehri[1], Kitty So[1], Allan Fong[1], Katelyn Shortt[1], Megan Webster[1], Femke Streijger[1], Andrew Macnab[1], Brian Kwon[1]

[1]University of British Columbia

Current clinical guidelines suggest augmenting the mean arterial pressure (MAP) of acute spinal cord injury (SCI) patients to increase spinal cord perfusion and preserve neurologic function. However, it is difficult for clinicians to hemodynamically manage acute SCI patients without real-time physiologic information about the effect of MAP augmentation within the injured cord. In this study, we developed an implantable optical sensor, based on Near Infrared Spectroscopy (NIRS), for non-invasive real-time monitoring of spinal cord tissue oxygenation and hemodynamics after acute SCI. Nine Yorkshire pigs received a T10 contusion/compression injury. A multi-wavelength NIRS system with a customized optical sensor was implanted extradurally at T9. To validate the NIRS measures, an invasive intraparenchymal (IP) O2/blood flow sensor was inserted directly into the spinal cord at T11. Using NIRS, the spinal cord tissue oxygenation percentage (TOI%) and concentrations of oxygenated, deoxygenated, and total hemoglobin were monitored after SCI. Episodes of MAP alterations were performed to simulate the types of hemodynamic changes SCI

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patients experience post-injury. The non-invasive NIRS sensor identified changes in spinal cord hemodynamics and oxygenation levels in all subjects, in which measurements correlated with the invasive IP sensor. This pre-clinical demonstration of the potential of NIRS is the first step in developing a clinically applicable device that spine surgeons can use to monitor spinal cord tissue hemodynamics post-injury and optimize clinical MAP management.

3-G-214 *Traumatic spinal cord injury and Indigenous persons: A mixed-methods pilot study to determine characteristics of a meaningful and relevant database in Ontario, Canada.*

Melanie Jeffrey[1], Sandra Juutilainen[1], Suzanne Stewart[1]

[1]University of Toronto

Trusting and navigating Western biomedical care is precarious for many First Nations persons. Specific barriers and facilitators to wellness for First Nations persons with traumatic spinal cord injury (TSCI) in Ontario are unknown. The effects of TSCI on Indigenous health are largely unrepresented in academic literature. Differences exist between urban, rural and remote communities' access to centres of excellence; differences may also differ within and between Indigenous cultures. We are developing a culturally-safe research space to interact with Indigenous persons in a mixed-methods study which will provide suggestions to improve the quality and relevance of existing TSCI healthcare databases for Indigenous persons living in Ontario. For our study, qualitative interview data will inform what quantitative healthcare data is analyzed, and future questions to be explored. Our network of collaborators in TSCI includes existing relationships with Indigenous persons and communities in diverse Ontario geographies. Our research will investigate urban, rural and remote Indigenous experiences of TSCI within this nest of relationships. General population TSCI data in matched regions will be used for comparison. Consultations with key experts have indicated that TSCI in general population databases in Ontario lack comprehensive data across the continuum of care. The results of this study may have broad implications the development of more inclusive health databases across Canada, with potential to improve service delivery for Indigenous and non-Indigenous persons.

3-G-215 *Inference of network connectivity using maximum entropy models*

Sara Mahallati[1], Milos Popovic[2], Taufik Valiante[3]

[1]IBBME, University of Toronto, [2]University Health Network, [3]Krembil research Institute, University Health Network

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Microcircuit level investigations of brain networks aim to link cellular measure of activity (ie. spikes) to collective dynamics (ie. brain oscillations). With our current ability to record from thousands of neurons, computational methods to understand collective neuronal activity (ie. as a network) are required. Maximum entropy models (MEM), are statistical models to describe such collective activity[1] where neuronal spiking (spike vs. no spike) is analogous to the spins states (up vs. down) of atoms in a ferromagnetic lattice. 'Connectivity' can then be inferred by solving the inverse Ising model for the coupling between neurons, which is a MEM constrained only by pair-wise correlations[2]. There is an ongoing debate on whether pairwise-based models are generalizable to neural systems at various spatial and temporal scales[3,4]. We thus assessed the reliability of the inverse Ising couplings as a proxy for connectivity to differentiate between different systems or network states. We tested the model on in silico inhibitory-excitatory spiking cortical networks using a range of synaptic delays, firing rates, and syncrony levels (ie. different types of collective behavior like oscillations vs. asynchronous firing). In addition, we evaluated the effect of two factors: spike train bin size, and spatial subsampling which affect the synaptic and propagation delays captured by the model, and the practical limits in real recordings respectively. This work thus benchmarks the network characteristics for which a connectivity reconstruction using inverse Ising models are reliable.

3-G-216 *Open-source software tools for relating neural activity to behaviour*

Nicholas Guilbeault[1], Jordan Guerguiev[1], Michael Martin[1], Tod Thiele[2]

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

Computational tools for analyzing behavioural and calcium imaging data are revolutionizing the field of systems neuroscience. Here, we present an open-source, easy-to-use software suite for analyzing behavioural and calcium imaging data. This collection of software performs closed and open-loop behavioural feedback, online and offline behavioural tracking, and calcium imaging analysis. We developed Bonsai packages for Allied Vision (USB3), Teledyne Dalsa (GigE) and Sentech (Camera Link) cameras to provide users with flexibility when building closed and open-loop behavioural assays. We provide Bonsai and Python software for rapid online and offline behavioural tracking, respectively. The tracking and feedback software extract heading direction, eye vergence angles, and tail curvature from videos of freely-swimming or head-fixed larval zebrafish. However, the software can be easily modified for non-aquatic model systems. Finally, we developed a calcium imaging analysis tool in Python, inspired by Suite2P, that offers users the Suite2P or the CaImAn calcium imaging analysis pipeline for performing motion correction and ROI segmentation. Our behavioural and calcium imaging analysis GUIs enable users to zoom into frames, plot behavioural data alongside calcium imaging data, process and visualize batches of videos, and rapidly curate tracking points and calcium imaging ROIs. In summary, our open-

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source, user-friendly collection of software programs combines the ability to dynamically control behaviour with the ability to relate neural activity to behaviour.

3-G-217 *Diffusion tensor imaging of the corpus callosum in healthy aging: investigating higher order polynomial regression modeling*

Wojciech Pietrasik[1], Ivor Cribben[1], Yushuan Huang[1], Fraser Olsen[1], Nikolai Malykhin[1]

[1]University of Alberta

Previous diffusion tensor imaging (DTI) studies confirmed the vulnerability of corpus callosum (CC) fibers to aging. However, most studies employed lower order regressions to study the relationship between age and white matter microstructure. The present study investigated whether higher order polynomial regression modeling can better describe the relationship between age and CC DTI metrics compared to lower order models in 140 healthy participants (ages 18-85). The CC was found to be non-uniformly affected by aging, with accelerated and earlier degradation occurring in anterior sections; callosal volume, fiber count, and fractional anisotropy decreased with age while mean, axial, and radial diffusivities increased. Higher order models improved the estimation of aging trajectory peaks and decline onsets, allowing for better trendline approximations; however, higher order regressions did not significantly improve the statistical measurement of age-associated decline when compared to lower order polynomial and linear models. In 14 of the 18 parameter values obtained, lower order models were equally proficient at describing the effects of age; linear models were equally proficient in 8 measures, including fractional anisotropy in all CC segments. The results suggest a marginal, primarily visual, improvement In DTI analysis with higher order models; higher order models may be unnecessary for CC DTI, with lower order and linear models providing sufficient power for measuring age-related declines.

H - History, teaching, public awareness and societal impacts in neuroscience

3-H-218 *Manual segmentation of hippocampal subfields from T-2 weighted MR imaging in a mouse model of stroke.*

Salman Khan[1], Stefan Koch[1], Susanne Mueller[1], Felix Knab[1], Katarzyna Winek[1], Andreas Meisel[1], Rene Bernard[1], Ulrich Dirnagl[1], Christoph Harms[1], Philipp Boehm-Sturm[1]

[1]Center for Stroke Research Berlin (CSB) and Charité University Medicine Berlin

Magnetic Resonance Imaging volumetric measurement is a useful tool to assess brain tissue damage after ischemic stroke. Mouse models of stroke have been developed to mimic clinical

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correlates. Non-invasive quantification techniques that can detect and follow the progression of disease are needed to identify underlying pathological substrates. We used T2-weighted MRI in a mouse model of intraluminal filament middle cerebral artery occlusion to determine hippocampal damage. Images were acquired with a small animal 7T MRI and image processing software. Axial T2-weighted images covering the distance between olfactory bulb and cerebellum were acquired with RARE sequences. Computer-aided planimetric assessment of the hippocampal lesion was performed by one blinded investigator. Ipsilateral and contralateral hippocampal volumes were determined on T2-weighted images with the use of image analysis software. After enlargement and optimal adjustment, the ipsilateral and contralateral hippocampus were traced and manually segmented on each slice with the use of the neuroanatomic landmarks on the mouse brain atlas. Hippocampal volumes were calculated from brain image slices by tracing regions of interest. The areas were then summed and multiplied by slice thickness. The lesion volume was calculated with and without edema correction and expressed as a percentage of the total hippocampal volume. Our goal was to provide proof of concept that small animal MRI is sufficiently sensitive to track subtle ischemic changes and provide quantitative assessment for infarct volume in the mouse brain.

3-H-219 *Scientific advocacy at Queen's University: Policy & neuroscience society*

Pauline Gaprielian[1], Jonathan Coutinho[1], Olivia Calancie[1]

[1]Queen's University

There is a growing need to employ evidence-based assessments of the impacts of social policies and efficacy of sustainable intervention strategies. Non-profit organizations (NPOs) are often required to collect data to evaluate the efficacy of their social policy interventions within the community. Furthermore, they are responsible to communicate their results to stakeholders on a variety of issues that they may not have expertise in. To fill in this knowledge gap, data scientists are hired to provide data analysis and visualization, and to communicate scientific results in lay language. Unfortunately, data scientists are costly and can often be out of reach of many NPOs. Graduate programs have the privilege to access academic resources that align with this feat (e.g., subscriptions to peer-reviewed scientific journals and data software programs). In an effort to contribute to scientific advocacy within our community, graduate students from Queen's University have developed a new club titled "Neuroscience & Policy Society," which aims to provide pro bono science to meaningful NPOs with social justice and health-related policy agendas. This club contains graduate students from a variety of departments working together to complete targeted literature reviews, data analysis, and reports in lay language for NPOs to communicate their results and have a greater understanding of the science underlying their

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cause. In an age where truth is too often discarded, we hope as students to improve the community by providing increased accessibility to scientific knowledge.

IBRO

3-IBRO-220 *CONTINUOUS spike wave of slow wave sleep: A case study*

soumia djirar[1], Paul Hwang[1]

[1]University of Toronto

Theme: Epilepsy Sleep Cycle Continuous spike wave of slow wave sleep: A case study Authors: Soumia Djirar, Colin Shapiro, Dragna Joven, Inna Voloh and Dr. Paul Hwang (Sponsoring member of CAN) This is the case of PM she is a 20 year right handed girl, from Gujrat India and first presented with dizziness and vomiting while sleeping. Onset of such events started one and a half year ago. She also cried in between and lost consciousness for 10 minutes duration. She suffered a partial seizure and parents started one year and a half ago. She first presented when she was five years and 3 months old. Pm is a 20-year-old Right handed girl who was followed for 16 years by the same Neurologist, had seizures onset at 1.5 years: Afebrile cpsz secondarily generalized with automatism, duration 5 minutes, recurrent every 2-5 weeks. Initial treatment consisted of PHT 12mg/kg, then CBZ 30 mg/kg+ VPA 18 mg/kg/day with improvement. SGA 2,7 kg at birth, 7-8 hours labour, "Right leg bent" at birth in India. Family history negative seizures. Initial development "normal": walked 12 months. Spoke Gujarati at 18 months, started ESL at four years old (JK, Can). EEG #1: 1.5 years old Generalized SWD L > R Dx POSZ not SFC. EEG #2: 4 years old Generalised irregular SED 2-3 Hz, DBA: secondary generalised epilepsy. EEG# 3: 6year old Epileptic encephalopathy with multiple independent spike foci; PSG c video This presentation describes the cycle of the various factors of the sleep epilepsy and learning development. An unusual cycle of the usage of ant-epileptics and sleep disorders that lead to

3-IBRO-221 *Genetic and nongenetic factors associated with cadasil: a retrospective cohort study*

Carolina Ospina[1], Carolina Ospina[1], Daniel Aguirre[2], Yesica Zuluaga-Castaño[2], Lina Velilla[2], Yakeel Quiroz[3], Francisco Lopera[2]

[1]Harvard University, [2]University of Antioquia, [3]Massachusetts General Hospital

Objective:To examine the relationships between genetic variables (genotype?phenotype) and cardiovascular risk factors in the natural history of CADASIL. Methods: This was a retrospective cohort study of 331 individuals with similar cultural and genetic backgrounds, 90 were carriers of four mutations in the NOTCH3 gene, and 231 were non-carrier family members. Cox proportional hazards models were fitted to estimate the effect of genetic and cardiovascular factors on the onset of first cerebrovascular event, and dementia. Competing risk regression models considered

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death as risk. Results: Noncarriers and NOTCH3 mutation carriers had similar frequencies for all cardiovascular risk factors, except hypercholesterolemia, which was more frequent in carriers (p = 0.007). Hypercholesterolemia (SHR 2.21, 95% CI 1.1?4.5) and diabetes (SHR 2.74, 95% CI 1.59?4.76) were associated with a younger age at onset of cerebrovascular events among carriers. Additionally, a genotype?phenotype relationship was observed among C455R mutation carriers, with higher frequency of migraines (100%), younger age at onset of migraine (median age 7 years, IR 8) and cerebrovascular events. Conclusions: This study characterizes extended family groups, allowing us a more robust comparison in the genotype?phenotype analysis and describes clinical evolution of both symptomatic and asymptomatic NOTCH3 carriers over time. The results suggest a complex interplay of genetic and cardiovascular risk factors that may help explain the variability in the clinical presentation and severity of CADASIL.

3-IBRO-222 *Deorphanization of Glossina f. fuscipes odorant receptors: toward decoding tsetse fly sense of smell*

Souleymane Diallo[1], Baldywn Torto[1], Daniel Masiga[1], Alan Christoffels[1], Merid Getahun[1]

[1]International Centre of Insect Physiology and Ecology

Insects in general rely on chemosensory receptors to detect chemical cues in their immediate environment. Therefore, understanding ligand-receptors interactions could be of great help for developing or improving the olfactory-based tool for vector control. To date, there is no information concerning ligand and odorant receptors interaction in tsetse fly, which is the main vector of African Trypanosomiasis. Hence, in this study we functionally characterize olfactory receptors in Glossina f. fuscipes. Recently, it has been shown that ligand-receptors interactions can be analysed after exposure to high concentration of relevant odorants. This approach known as DREAM (Deorphanization of receptors based of on expression alterations in mRNA levels) has been used in this study to analyze change in odorant receptors expression after exposure to six chemicals (Repellents: Deltaoctalactone, Geranylacetone, Pentanoic acid, Guaiacol and attractant: 1-octen-3-ol). We were able to identify ligand-receptors pairing in 32 odorants receptors. The odorant receptors were found to be more generalist wish could be explained by the high concentration of the odorant [10]-3) dilution used for the exposure. Interestingly, the PCA analysis clustered the responses profile of the odorants receptors to repellent and to the attractant molecule differently. In silico prediction of the binding site could be necessary to validate our findings. This study provides an initial functional analysis of Glossina f. fuscipes odorants receptors that are involved in tsetse repellent detection and creates an opportunity to understand tsetse flies sense of smell. Key words: Glossina, ORs, DREAM, deorphanization, odorants, olfactory sensory neurons.

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3-IBRO-223 *Antioxidant and apoptosis-inhibition potential of Carpobrotus edulis in a model of Parkinson's disease*

Adaze Enogieru[1], Sylvester Omoruyi[2], Okobi Ekpo[2]

[1]University of Benin, [2]University of the Western Cape

Parkinson's disease (PD) is a neurological disorder resulting from the progressive loss of dopaminergic neurons. Presently, there is no cure for PD, and the search for complementary and alternative medicines capable of halting dopaminergic neuronal degeneration is valid. In traditional medicine, Carpobrotus edulis (CE) is used to treat such conditions as tuberculosis, diabetes mellitus and constipation. It is believed that this plant possesses some bioactive compounds responsible for its biological activities. Accordingly, we evaluated the protective effects of CE against 1-methyl-4-phenylpyridinium (MPP+)-induced toxicity in the dopaminergic SH-SY5Y cell line, as well as its underlying mechanism. SH-SY5Y cells were treated with varying concentrations of CE and MPP+ respectively to determine the optimal concentrations of MPP+ and CE for further experiments. Thereafter, SH-SY5Y cells were pretreated with 30 µg of CE before treatment with 2 mM of MPP+ to induce cellular damage. MTT assay was performed to evaluate cellular viability; flow cytometry was utilized to assess intracellular reactive oxygen species (ROS) production, Hoechst nuclear staining was used to visualize apoptosis and assay kits were used to investigate the activity of caspases 3/7 and 9. MPP+ treatment induced a loss of cell viability, increased the number of condensed nuclei and apoptotic cells, increased ROS production, initiated caspase 9 and activated caspase 3/7. Conversely, the effects of MPP+-induced toxicity were attenuated by the pretreatment of SH-SY5Y cells with 30 µg of CE. The protective effects of CE against MPP+-induced toxicity in SH-SY5Y cells may be attributed to its antioxidant and antiapoptotic properties.

3-IBRO-224 *Construction and use of regulatable adenovectors expressing the Yamanaka genes (OSKM) for implementing regenerative medicine in the aging brain*

Marianne Lehmann[1], Martina Canatelli-Mallat[1], Priscila Chiavellini[1], Gustavo Morel[1], Goya Rodolfo[1]

[1]Institute for Biochemical Research (INIBIOLP) Histology B & Pathology B, School of Medicine

Biological rejuvenation by partial cell reprogramming is an emerging avenue of research. In this context, regulatable pluripotency gene expression systems are the most widely used at present. We constructed a regulatable bidirectional adenovector expressing Green Fluorescent Protein (GFP) and oct4, sox2, klf4 and c-myc (OSKM) genes. The OSKM genes are arranged as a bicistronic tandem (hSTEMCCA tandem) which is under the control of a Tet-Off bidirectional promoter that also controls the expression of the GFP gene. Separately, a constitutive cassette expresses the regulatory protein tTA. Vector DNA was transfected in HEK293 Cre cells, which were additionally infected with the helper adenovector H14, unable to package its DNA due to the

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Cre recombinase produced by the HEK293 Cre cells. The newly-generated vector was expanded by 5 iterated co-infections of the above cells and the adenovector purified by ultracentrifugation in a CsCl gradient. The titer of our preparation was 1.2 x 1012 physical viral particles/ml. As expected, GFP fluorescence in vector-transduced rat fibroblast cultures declined with the dose of doxycycline (DOX) present in the medium. Immunocytochemical analysis of transduced cells confirmed the expression of the 4 Yamanaka genes. Additionally, three days after vector injection in the hypothalamus of rats, a significant level of fluorescence was observed in the region. Addition of 2 mg/ml DOX to the drinking water reduced GFP expression. This adenovector constitutes a promising tool for implementing non-integrative partial cell reprogramming.

3-IBRO-225 *Role of succinate/suncr1 signalling pathway in paclitaxel-induced neuropathic pain*

Francisco Isaac Fernandes Gomes[1], Ricardo Kusuda[1], Rafaela Guimarães[1], Alexandre Pereira Lopes[1], Nicole da Silva[1], Fernando Cunha[1], Thiago Cunha[2]

[1]Ribeirao Preto Medical School - University of Sao Paulo, [2]University of Sao Paulo

This study aimed to characterise the role of succinate/Suncr1 signalling pathway in the development of paclitaxel-induced peripheral neuropathy. C57Bl/6 wildtype and Suncr1 full knockout (Suncr1-/-) mice received four alternate doses of paclitaxel (8mg/kg; i.p.) and behavioural tests were performed using von Frey filaments and acetone test. In another experimental series, mice were treated with paclitaxel as described and sciatic nerve and dorsal root ganglion (DRG) samples were harvested for qRT-PCR for GPR91 and tricarboxylic acid cycle (TCA) enzymes, as well as pro- and anti-inflammatory cytokines. Suncr1-/- mice were protected from paclitaxel-induced neuropathic pain (mechanical allodynia and cold hypersensitivity). It was also found an increased expression of Suncr1 gene in the DRGs as well as the same pattern was observed for gene expression of TCA enzymes after paclitaxel administration. Our findings suggest that succinate through Suncr1 can act as a pro-nociceptive factor that contributes to the development of paclitaxel-induced peripheral neuropathic pain. Keywords: paclitaxel; neuropathy; succinate; GPR91. Financial support: Center for Research in Inflammatory Diseases-CRID (FAPESP 13/08216-2) and FAPESP Scholarship (2017/23815-0).

3-IBRO-226 *Triggering reconsolidation of an ethanol conditioned place preference (CPP) memory: the role of reactivation`s length and dopaminergic receptors*

Flávia Boos[1], Cristiane Favoretto[1], Isabel Quadros[1]

[1]Federal University of São Paulo

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Following recall, memory can enter in a labile state (labilization, LAB) and be updated through the reconsolidation process. It has been proposed that occurrence of prediction error during recall is important to induce LAB, which involves dopamine (DA) signaling. In the CPP literature, reactivation sessions successful to induce LAB are conducted in a drug-free state. Importantly, studies suggest that DA can be either increased by contextual cues related to the drug or decreased by prediction error if the drug was absent. Here, our goal was to study the involvement of D1R in LAB of a CPP memory. To investigate this, we conditioned mice to CPP with ethanol and later reactivated memory by allowing them to freely explore the contexts in a drug-free state for 5 or 10min. Immediately after, animals receive the protein synthesis inhibitor cicloheximide (CHX) to block reconsolidation, or vehicle (VEH). Next, to assess the D1R involvement in memory LAB, we repeated the same protocol but also administered the D1R antagonist SCH23390, D1R agonist SKF38393, or VEH i.p. 30min before reactivation. We found that CHX disrupted reconsolidation when injected after the 10min reactivation session, but not after the 5min one. In the second experiment, SCH and SKF treatments did not affect recall, and the 10min session unexpectedly decreased preference in most of the groups during test, including VEH-VEH, suggesting that extinction took place. These preliminary results indicate that the CPP memory is not labilized by a 5min reexposure, but reconsolidation is triggered following a longer 10 min session. However, a 10min reactivation may be in between the time window effective to induce reconsolidation and extinction, and additional studies will be required to infer the role of D1R in LAB.

Poster cluster: Sustained effects of general anesthetics: missing links for GABAA

3-Cluster-227 *Does insufficient BDNF contribute to cognitive impairment after general anesthesia?*

Ali Alavian-Ghavanini[1], Marc Anthony Manzo[1], Dian-shi Wang[1], Beverley Orser[1]

[1]University of Toronto

General anesthetic drugs likely contribute to persistent cognitive impairment that occurs in some postoperative patients. We showed that anesthetic drugs trigger a sustained overexpression of extrasynaptic GABAA receptors in neurons, which causes cognitive deficits in mice. Pharmacologically increasing the level of brain-derived neurotrophic factor (BDNF) in the brain prevents such receptor overexpression and attenuates cognitive deficits. Others showed that exposing immature mice to general anesthetic drugs causes a sustained decrease in BDNF levels in the brain. We aimed to determine whether clinically relevant doses of general anesthetics cause a persistent decrease of BDNF in the brains of adult mice and whether this decrease contributes to cognitive impairment. Adult mice were exposed to isoflurane (1.3% for 1 hr) and 1- and 7-days post-treatment, BDNF mRNA and protein levels were measured in the hippocampus. The results

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showed that BDNF mRNA levels decreased 25% and 80% 1- and 7-days after exposure, respectively. Protein levels of BDNF were also reduced. Future studies will examine the time course of recovery of BDNF levels after anesthesia, the mechanisms underlying the reduction of BDNF, and whether this reduction contributes to persistent cognitive impairment. Our findings will delineate reduced BDNF as a biomarker and identify new potential therapeutic targets to mitigate cognitive impairment after general anesthesia.

3-Cluster-228 *Anesthetic activation of GABAA receptors in astrocytes persistently increases a tonic inhibitory current in neurons via an IL-1β and p38 MAPK pathway*

Arsène Pinguelo[1], Kirusanthy Kaneshwaran[1], Dian-shi Wang[1], Beverley Orser[1]

[1]University of Toronto

Brief exposure to a general anesthetic drug triggers a sustained increase in tonic current generated by GABAA receptors (GABAARs) in hippocampal neurons, which causes persistent cognitive deficits. Astrocytes are necessary for this effect; however, the underlying mechanisms are unknown. Interestingly, this tonic current in hippocampal neurons is also increased by IL-1β via a p38 mitogen-activated protein kinase (p38 MAPK) pathway. As astrocytes express GABAARs, we postulated that anesthetic drugs activate GABAARs in astrocytes, which triggers a sustained increase in GABAAR function in neurons through an IL-1β and p38 MAPK signaling pathway. To test this hypothesis, cultures of astrocytes and neurons were prepared from fetal mice. Astrocytes were treated with etomidate /- a GABAAR antagonist bicuculline for 1 h then washed. Two hours later, astrocyte conditioned media was collected and applied to cultured neurons and 24 h later, tonic current was recorded with voltage clamp techniques. Inhibitors of IL-1 receptor (IL-1ra) or p38 MAPK (SB203,580) were added to the astrocyte conditioned medium in some studies. Results showed that bicuculline, IL-1ra and SB203,580 prevented the anesthetic-induced persistent increase in tonic current in neurons. Thus, activation of GABAARs in astrocytes triggers a sustained increase in tonic current in neurons via an IL-1β and p38 MAPK pathway. These results identify a signaling pathway that might be targeted to mitigate cognitive deficits after general anesthesia.

3-Cluster-229 *Comparing negative allosteric modulators of alpha5GABAA receptors for inhibition of a tonic current in primary hippocampal neurons*

Marc Anthony Manzo[1], Winston Li[1], Dian-shi Wang[1], Beverley Orser[1]

[1]University of Toronto

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Excessive function of alpha5 subunit-containing GABAA receptors (a5GABAARs) has been implicated in several neurocognitive disorders including depression, stroke, Alzheimer's disease, and perioperative neurocognitive disorder. a5GABAARs generate a persistent inhibitory current or "tonic current" that disrupts cognitive function. Several negative allosteric modulators of a5GABAARs (a5-NAMs) have been developed as cognitive-enhancing drugs. While the efficacy of a5-NAMs has been studied using recombinantly expressed GABAARs, few studies have examined their effects on native GABAARs in primary neurons. This study compared the inhibitory effects of four a5-NAMs (L-655,708, MRK-016, a5IA, and basmisanil) on the amplitude of a tonic current recorded in cultured hippocampal neurons. Cultures were prepared from fetal mice and the tonic current was recorded using whole-cell voltage clamp techniques. Preliminary results showed that L-655,708 (20 nM) caused a greater inhibition of the tonic current (31 ± 7%, mean ± SEM, n = 12) than MRK-016 (100 nM, 24 ± 6%, n = 10). Interestingly, basmisanil caused both an increase and a decrease in the amplitude of the tonic current in a cell-specific manner. Future studies will compare the effects of a5IA. These results will advance the development of a5-NAMs that may be used to treat neurocognitive disorders in patients.

3-Cluster-230 *Ketamine prevents an anesthetic-triggered persistent hyperactivity of GABAA receptors via NMDA receptor-independent mechanisms*

Winston Li[1], Agnes Crnic[1], Dian-shi Wang[1], Beverley Orser[1]

[1]University of Toronto

Postoperative cognitive deficits are associated with poor long-term outcomes and substantial increases in healthcare costs. The etiology of such deficits is likely multifactorial; however, anesthetic drugs are a contributing factor. We previously showed that anesthetic drugs trigger a sustained increase in cell-surface expression and function of extrasynaptic GABAA receptors and this increase contributes to cognitive deficits. Interestingly, ketamine has been shown to attenuate postoperative cognitive deficits in patients. Thus, we hypothesize that co-treatment with ketamine prevents the anesthetic-induced persistent hyperactivity of extrasynaptic GABAA receptors. Also, since NMDA receptors are the canonical target for ketamine, we postulate that ketamine prevents hyperactivity of GABAA receptors by inhibiting NMDA receptors. Cocultures of hippocampal neurons and cortical astrocytes are treated for 1 h with the anesthetic drug etomidate +/- ketamine, APV, or memantine; then washed. After 24 h, GABAA receptor function was studied by recording whole-cell voltage clamp currents from hippocampal neurons. The results show that etomidate increased a tonic current generated by GABAA receptors, and co-treatment with ketamine prevents this increase. The NMDA receptor antagonists APV and memantine failed to prevent the increase. In conclusion, ketamine prevents the etomidate-induced persistent increase in receptor activity, through an NMDA receptor-independent mechanism. This novel mechanism may account for the cognition-sparing properties of ketamine.

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3-Cluster-231 *The 'double hit' of inflammation and general anesthesia causes persistent cognitive impairment in mice*

Shahin Khodaei[1], Raza Syed[1], Dian-shi Wang[1], Beverley Orser[1]

[1]University of Toronto

Background: Many patients experience postoperative cognitive impairment, through mechanisms that are poorly understood. Interestingly, not all patients develop such deficits, suggesting that predisposing factors such as inflammation are important. Preclinical findings show that anesthetic drugs contribute to the development of postoperative cognitive impairment. Here, we test the hypothesis that inflammation and anesthesia interact to markedly impair cognition in mice. Methods: Adult male C57BL/6 mice were injected with lipopolysaccharide (LPS; 1.0 mg/kg, i.p.) to induce inflammation. Twenty-four hours later, mice were treated with a general anesthetic drug etomidate (20 mg/kg, i.p.). Over the next 4 days, the novel object recognition (NOR) and the 3-day puzzle box assays were used to assess recognition memory and executive function respectively. Results: In the NOR task, LPS but not etomidate alone impaired recognition memory. The combination of LPS and etomidate caused memory deficits similar to LPS alone. In the puzzle box assay, mice treated with LPS or etomidate alone showed no impairment in executive function whereas those treated with the double hit were impaired. Conclusions: Memory was impaired in all LPS-treated mice suggesting a ceiling effect. In contrast, the double hit of inflammation and etomidate caused deficits in executive function that were not observed in mice treated with LPS or etomidate alone. Ongoing studies will study a lower dose of LPS and the molecular mechanisms underlying the deficits caused by the double hit of inflammation and etomidate.

Poster cluster: Using MRI to index memory differences across the lifespan

3-Cluster-232 *Estimating Alzheimer's risk from memory performance*

Sheida Rabipour[1], Elsa Yu[1], Sricharana Rajagopal[1], Stamatoula Pasvanis[1], John Breitner[1], M. Natasha Rajah[1]

[1]McGill University

Age-related episodic memory decline negatively impacts older adults' quality of life, can lead to a loss of independence, and represent one of the hallmarks of late-onset Alzheimer's Disease (AD). Despite the prevalence and burden of such decline, treatments are scarce. A promising approach is to identify older adults at risk of AD, showing early differences in memory-related brain function. These people may best benefit from early entry into currently available treatments. We sought to examine the potential influence of having an apolipoprotein E ε4 allele (+APOE4), on whole-brain

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activity during an episodic memory task in healthy older adults with family history of AD. Functional magnetic resonance images were acquired from 180 older adults (63.14 ± 5.24 years of age; 131 women) during performance of a task requiring memory of objects in their spatial context. We performed behavioral Partial Least Squares to evaluate correlations between performance and whole-brain task-related activation in +APOE4 and -APOE4 individuals. We found significant correlations between fronto-parietal activity and object and source recall in -APOE4. Patterns were reversed in +APOE4, and were particularly prominent during encoding of subsequently recognized items and correct source retrieval. Our results suggest that source recall and object recognition may associate with different neural substrates in -APOE4 vs. +APOE4 individuals. These findings provide a new perspective on potential differences in brain-behavior relationships based on genetic composure in people with family history of AD.

3-Cluster-233 *Age- and reserve-related increases in fronto-parietal and anterior hippocampal activity during episodic encoding predict subsequent memory*

Abdel Elshiekh[1], Sricharana Rajagopal[1], Stamatoula Pasvanis[1], Elizabeth Ankudowich[1], Maria Rajah[1]

[1]McGill University

Remembering associations between encoded items and their contextual setting is a feature of episodic memory. Although this ability deteriorates with age, evidence suggests that some older adults exhibit preserved memory. In this fMRI study, we examined how general cognitive ability as indexed by neuropsychological testing and cognitive reserve (education and intelligence) informs episodic memory performance and brain activity patterns across the adult lifespan. We used multivariate Behavioural Partial Least Squares (B-PLS) to identify how age, cognitive ability, and/or episodic memory accuracy were related to brain activity patterns during easy and hard episodic encoding and retrieval events in 154 adults (age range: 19-76 yrs). Results showed that activity in ventral visual, inferior parietal and parahippocampal regions increased with age, cognitive ability, and accuracy during easy associative encoding tasks. This suggests that higher cognitive ability/reserve may mitigate age-related decline through enhanced recruitment of some brain regions at lower levels of task difficulty.

3-Cluster-234 *Using brain cortical thickness to predict chronological age: evidence from an adult lifespan sample*

Sivaniya Subramaniapillai[1], A. Ross Otto[1], Sricharana Rajagopal[1], Stamatoula Pasvanis[1], M. Natasha Rajah[1]

[1]McGill University

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Healthy aging is associated with widespread declines in cortical thickness (CT). Moreover, there is variability in the effect of age on CT. Studies have suggested that individuals' life experiences (cognitive reserve, e.g., education) can play a significant role in contributing to one's brain health. The present adult lifespan (20-76 years, N = 151) study tested the hypothesis that the CT of specific ROIs can be used to successfully predict chronological age. CT was computed using the CIVET 2.1.10 automated preprocessing pipeline, which rendered a CT estimate at 81924 points across the cortex. The Desikan-Killian Atlas was then used to obtain the mean CT value for each subject for a set of 64 ROIs. We used a ridge regression model on the training dataset (N=107) to derive the optimal tuning (lambda) parameter. This lambda parameter, determined through 10-fold cross-validation, was used in another ridge model to predict subjects' chronological age using the testing (N= 44) dataset. Brain age, defined as the mean CT of specific ROIs, predicted chronological age at 80% (classification accuracy). The top predictors of the model, bilateral prefrontal cortex, right precuneus, and left occipital cortex, exhibited a general age-related decline. Additionally, a greater level of education was associated with a lower predicted age. Thus, it is possible that education level might act as a cognitive reserve factor by mitigating the effects of age-related neural decline, and contributing to brain maintenance in healthy aging.

3-Cluster-235 *Anterior and posterior memory systems differentially predict associative and recognition memory in young adults*

Jamie Snytte[1], Abdel Elshiekh[1], Sivaniya Subramaniapillai[1], Lyssa Manning[1], Rosanna Olsen[2], Natasha Rajah[1]

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

The medial temporal lobes (MTL) play an important role in episodic memory. Recent research suggests two distinct memory networks that differentially support episodic memory for items (anterior memory system), compared to memory for contextual associations (posterior memory system). In the current study we tested whether individual differences in gray matter volume of MTL regions and cortical thickness of non-MTL regions of the anterior vs. posterior memory systems differentially predict item-recognition vs. contextual memory in young adults. We used the OAP protocol and the MAGeT Brain algorithm for segmentation of PRC, ERC, antHC, postHC and PHC, and CIVET 2.1.0 for automated cortical thickness extraction at each region of the AAL atlas. Verbal item memory measures were obtained from the delayed recognition component of the CVLT. Object-recognition and object-location memory measures were obtained from an object-location associative memory task. The anterior model predicted a significant proportion of the variance in verbal-recognition memory, but not object-recognition memory or associative object memory ($p = 0.02$, $R^2 = 0.498$). The posterior model predicted a significant proportion of the variance in contextual object-location memory, but not verbal-recognition or object-recognition memory ($p = 0.012$, $R^2 = 0.580$). Our results support the notion of distinct anterior and

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posterior memory systems, suggesting a gradient along the MTL and the cortex, where anterior structures are involved in familiarity processing and posterior regions are involved in associative processing.

Poster cluster: Vulnerable brain laboratory

3-Cluster-236 *A novel perspective on white matter inflammation following a permanent middle cerebral artery occlusion in Wistar rats*

Berk Rasheed[1], Rishika Geda[1], Romit Bhusari[1], Elena Hachinski[1], Omar Eldash[1], Shawn Whitehead[2]

[1]University of Western Ontario, [2]Western University

Strokes that involve the middle cerebral artery (MCA) are the most prevalent among clinical stroke cases. Previous research suggests that white matter inflammation (WMI) is a core feature of post-stroke pathology and that it may result in secondary cognitive impairments. WMI has been demonstrated in chronic stroke models to spread across white matter tracts and can cross over from the site of injury to the contralateral hemisphere. However, there remains uncertainty as to how and when WMI develops post-stroke. In a rat model using 8-week-old male and female Wistar rats, it was hypothesized that WMI would be present in the ipsilateral and contralateral white matter tracts following an acute stroke. A permanent MCA occlusion was induced using diathermy forceps and inflammation was assessed 4 days later. Using OX6 as an indicator of WMI, which immunohistochemically marks for M1-activated microglia, it was found that WMI was only present in the contralateral corpus callosum, and that there was no OX6 signal in the ipsilateral corpus callosum. There was also an increase in IgG in the ipsilateral corpus callosum, but not in the contralateral corpus callosum. These results suggest that IgG could be a chemorepulsant agent for M1 activated microglia. A comprehensive understanding of the chronological development of MCA stroke pathology should provide new insights to the role of WMI in MCA stroke. WMI may be a target of therapeutic treatment once its mechanisms are better understood.

3-Cluster-237 *Arteriole and venule collagenosis and density alterations within post mortem white matter hyperintensities and periventricular infarction in aging, cerebrovascular and Alzheimer's disease*

Austyn Roseborough[1], Kristopher Langdon[1], Robert Hammond[1], Stephen Pasternak[2], Ali Khan[3], Shawn Whitehead[1]

[1]Western University, [2]Robarts Research Institute, [3]University of Western Ontario

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Cerebral small vessel disease (SVD) affects the microvasculature of the brain, associating with cognitive decline and dementia. SVD is visualized by hyperintense regions within the white matter (WMH) on magnetic resonance imaging (MRI). Periventricular WMH within the frontal lobe specifically may have a negative effect on executive functions. Executive dysfunction represents a set of cognitive changes, including processing speed and attention, that can precede memory impairment in Alzheimer disease. The etiology and development of cerebral small vessel disease and its relation to executive dysfunction is not well understood. In this study we sought to characterize alteration within the microvasculature of the periventricular frontal white matter. 7-Tesla MR imaging of formalin-fixed coronal brain sections was performed on 20 brains with a neuropathological diagnosis of normal, cerebrovascular disease or Alzheimer disease. Stenosis within small, medium and large venules and arterioles was calculated within both the periventricular and subcortical white matter. Stenosis of the small (<50 um diameter) arterioles and venules within the periventricular white matter specifically was associated with increased severity of periventricular WMH and the presence of periventricular infarction. Vessels were examined for the presence of vascular amyloid deposition and evidence of blood brain barrier dysfunction. Further study of the cellular changes that underlie microvascular damage within the white matter is required to understand the impact of SVD plays in aging and cognitive decline.

3-Cluster-238 *Autonomic mechanisms underlying post-stroke cardiac dysfunction in the insular ischemic stroke rat model*

Victoria Jaremek[1], Brittany Balint[1], Victoria Thorburn[1], Thomas Milazzo[1], Lynn Wang[1], Shawn Whitehead[1], Luciano Sposato[2]

[1]Western University, [2]Schulich School of Medicine and Dentistry

Patients who have suffered an ischemic stroke with damage to the right insular cortex (IC) frequently develop post-stroke myocardial complications. However, the pathophysiology of these post-stroke cardiac changes requires additional investigation which is complicated by a lack of pre-clinical models. Further, whether post-stroke cardiac dysfunction is due to autonomic dysregulation following stroke is unknown. IC ischemic stroke was induced in 6-month-old male Wistar rats via unilateral stereotaxic injection of endothelin-1 (ET-1) into right or left IC. Control rats received a phosphate-buffered saline (PBS) injection. Hearts were histologically examined at 28 days post-stroke for inflammation (CD68 , CD3 , CD45 , myeloperoxidase, CD45R, immunostaining) and fibrosis (Masson's Trichrome stain). Areas of interest included the 4 heart chambers and left atrial/pulmonary vein border (LA-PV border), an area of enriched autonomic innervation. Brainstem areas relay autonomic information to the heart, thus GFAP, NeuN and OX-6 immunostaining was performed to identify reactive astrocytes, neurons and activated microglia, respectively. Brainstems were analyzed at the level of the medulla, pons and midbrain. LA-PV border tissue inflammation and fibrosis were increased 28 days following stroke induction.

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Preliminary results from the study suggest increased brainstem neuroinflammation, specifically at the nucleus of the solitary tract 28 days post-stroke. These findings provide insight into the pathophysiological mechanisms that may underlie post-stroke cardiac dysfunction.

3-Cluster-239 *Transgenic rat model of Alzheimer's disease develop deficits in cognition and widespread neuroinflammation with age*

Qingfan Liu[1], Nina Weishaupt[1], Sheojung Shin[1], Ramandeep Singh[1], Yuksel Agca[2], Cansu Agca[2], Vladimir Hachinski[1], Shawn Whitehead[3]

[1]Vulnerable Brain Laboratory, Schulich School of Medicine and Dentistry, Western University, [2]University of Missouri, [3]Western University

Background: Animal models commonly used in preclinical Alzheimer's disease (AD) research largely fail to address the pathophysiology, including the impact of known risk factors, of the sporadic form of the disease. Here, we used a transgenic rat (APP21) that does not develop AD-like pathology spontaneously with age but does develop pathology following vascular stress. APP21 rats were characterized behaviorally and histologically up to 19 months of age. Methods: The open field test was used to measure activity. The Morris water maze was used to assess learning, memory, and strategy shift. Neuronal loss and microglia activation were assessed throughout the brain. Results: APP21 rats showed deficits in working memory from an early age, yet memory recall performance after 24 and 72 h was equal to that of wildtype rats and did not deteriorate with age. A deficit in strategy shift was observed at 19 months of age in APP21 rats compared to wildtype rats. Histologically, APP21 rats demonstrated accelerated white matter inflammation compared to wildtype rats, but no differences in neuron loss were observed. Conclusions: The presence of white matter pathology and executive function deficits mirror what is found in patients with mild cognitive impairment or early dementia. This rat model will be useful for translationally meaningful studies into the development and prevention of sporadic AD. The presence of widespread white matter inflammation, as the only observed pathological correlate for cognitive deficits, raises questions as to the role of neuroinflammation in cognitive decline.

3-Cluster-240 *Enhancement of ganglioside signal in MALDI MS imaging of formalin fixed human brain tissue*

Aaron Harris[1], Austyn Roseborough[1], Rahul Mor[1], Shawn Whitehead[1]

[1]Western University

Matrix assisted laser desorption ionization (MALDI) imaging mass spectrometry (IMS) is used to perform mass spectrometric analysis directly on biological samples providing accurate visual and

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anatomical spatial information of molecules within tissues. A current obscuration of MALDI-IMS is that it is largely performed on fresh frozen tissue whereas clinical tissue samples stored long term are fixed in formalin, and the fixation process is thought to cause signal suppression for lipid molecules. Studies have shown that fresh frozen tissue sections applied with an ammonium formate (AF) wash prior to matrix application in the MALDI-IMS procedure display an increase in observed signal intensity and sensitivity for lipid molecules detected in the brain while maintaining the spatial distribution of molecules throughout the tissue. In this work we investigate the effectiveness of an AF wash on post-fixed rat and human brain tissue sections in an effort to increase the viability of formalin fixed tissue imaging in a clinical setting. Results herein demonstrate that the AF wash significantly improved MALDI-IMS spectra for gangliosides, including GM1 in fresh frozen rat brain, formalin-fixed rat brain and formalin fixed human brain samples. AF wash also demonstrated improvements in MALDI-IMS image quality while retaining the spatial distribution of molecules. Results indicate that this method will allow analysis of gangliosides from formalin-fixed clinical samples, which can open additional avenues for neurodegenerative disease research.

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